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Tetrahedron
Tetrahedron 64 (2008) 949–968
www.elsevier.com/locate/tet

Central-to-axial chirality transfer in the benzannulation reaction of optically pure Fischer carbene complexes in the synthesis of allocolchicinoids

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Received 5 September 2007; received in revised form 25 October 2007; accepted 26 October 2007

Abstract

A method for the synthesis of allocolchicinoids is explored that involves the benzannulation reaction of Fischer chromium carbene complexes with alkynes. The benzannulation reaction is employed to install the aromatic C-ring via the reaction of an α,β-unsaturated carbene complex in which the carbene complex is attached to a seven-membered ring that is to become the B-ring of the allocolchicinoids. Two different regioisomeric series can be accessed depending on which position the carbene complex is on the seven-membered ring. A key issue that is addressed is the stereochemistry of the newly formed axis of chirality that results from a stereo-relay from an existing chiral center on the seven-membered ring at the position destined to be C(7) in the allocolchicinoids. The level of stereochemistry is dependent on the position of the carbene complex on the seven-membered ring. A mechanism is proposed to account for this stereochemical dependence and to account for the observed effects of temperature and solvent on the stereoselectivity. Finally, the benzannulation reactions of optically pure complexes are examined and quite surprisingly one, but not both, of the diastereomeric products is racemized. The racemization can be prevented with the proper choice of solvent and temperature. A mechanism is proposed to account for the racemization of only one of the diastereomers of the product that involves the intermediacy of an *o*-quinone methide chromium tricarbonyl complex.

1. Introduction

Allocolchicine (−)-**1** was isolated from *Colchicum cornigerum* and from the flowers *Colchicum autumnale*.[1] Like colchicine, allocolchicine is tubulin-interactive agent that is capable of blocking cell proliferation.[2] Other naturally occurring allocolchicinoids include androbiphenyline ((−)-**4**), colchibiphenyline ((−)-**5**), salimine ((−)-**2**), jerusalemine ((−)-**3**) and (−)-suhailamine (Scheme 1). Alkaloids **4** and **5** were isolated from *Colchicum ritchii*;[3] (−)-**2**, (−)-**3**, and (−)-suhailamine—from *Colchicum decaisnei* Boiss.,[4] both being middle eastern species. The structure (−)-**1** has been assigned to (−)-suhailamine, but its spectroscopic and physical properties didn't match those of the authentic sample of (−)-**1**.[5] At this point the true structure of (−)-suhailamine remains unclear. Two total syntheses of (−)-allocolchichine have been reported[6] and a number of syntheses of allocolchicinoids and allocolchicine derivatives have also been described.[5,7]

Allocolchicinoids display molecular asymmetry resulting from a noncoplanar arrangement of the rings A and C.[2,8] The rings are twisted with a torsion angle of about 53−55°. The major rotamer of natural (−)-(7*S*)-**1** has its acetamido group in pseudoequatorial position. This is consistent with an a*R* axial configuration. For (−)-allocolchicine **1** the (a*R*,7*S*) conformation is generally more preferred than the (a*S*,7*S*) conformation (Scheme 1). In solutions of allocolchicinoids the equilibrium position also depends on the nature of C(7) substituent and on the solvent polarity. It is not clear whether the predominant (a*R*,7*S*) conformation or a small amount of the (a*S*,7*S*) form, present in equilibrium, is active in tubulin-binding processes. For this reason, we set out to prepare allocolchicinoids in which the conformations were locked in the (a*R*,7*S*) and (a*S*,7*S*) conformations. We have previously reported that the benzannulation reaction of the carbene

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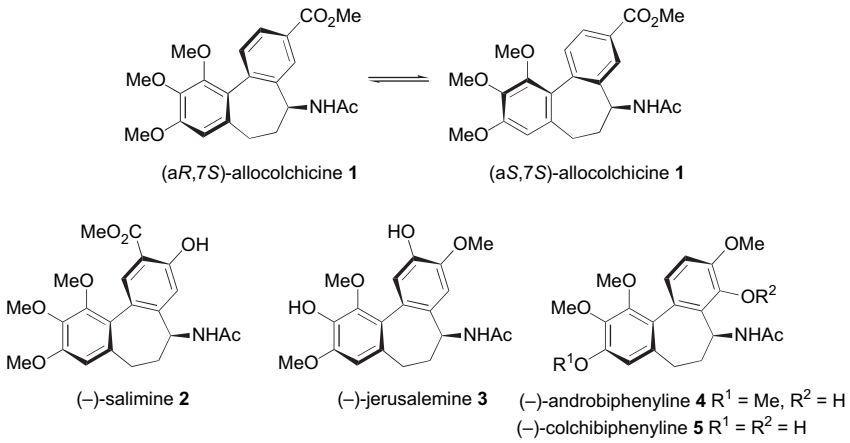
doi:10.1016/j.tet.2007.10.115



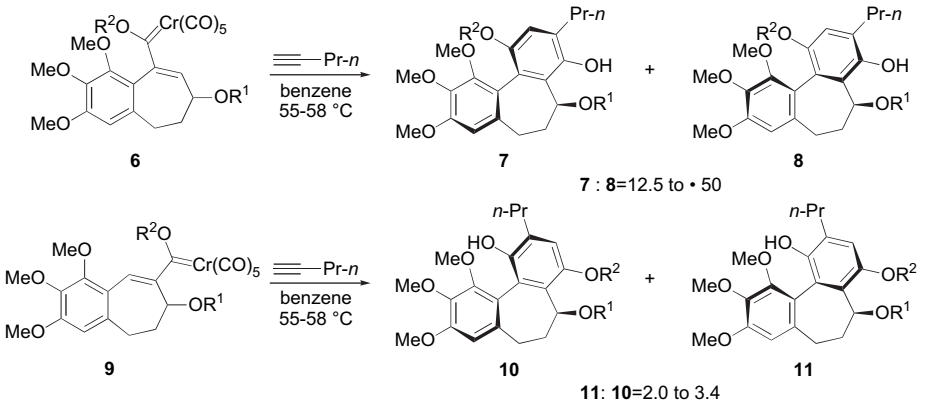
Scheme 1.

complexes **6** and **9** with 1-pentyne gives diastereomeric products (**7**,**8** and **10**,**11**, respectively, Scheme 2) as the result of the formation of an axis of chirality when the new benzene ring is being annulated.[9] The barrier to interconversion about the chiral biaryl axis in these molecules is much higher than for allocolchicine. The diastereomers **7** and **8** and **10** and **11** can be separated and their interconversion can only be effected when heated to greater than 150 °C.[10] In the present work, we present a more extensive examination of the benzannulations of carbene complexes **6** and **9** with a 1-pentyne and with a number of other alkynes and report on the synthesis of optical pure carbene complexes **6** and **9** and their reactions with 1-pentyne.

2. Results and discussion

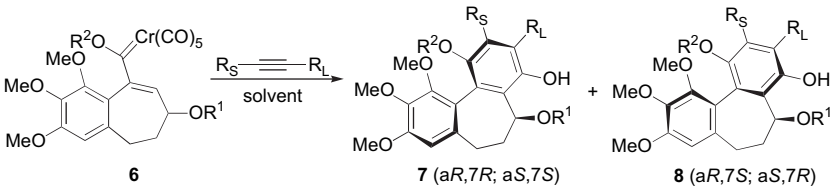
The reactions of carbene complexes **6** and **9** were examined with various alkynes followed by oxidative demetalation (Tables 1 and 2).[9] In most cases, phenolic allocolchicinoids (**7** and **8** or **10** and **11**) were formed as major products. The barrier to the rotation about the biaryl bond in **7**, **8**, **10**, **11** is higher than in the natural allocolchicinoids, which permits the isolation of the configurationally stable (a*R*,7*S*; a*S*,7*R*) and (a*R*,7*R*; a*S*,7*S*) atropisomers. Diastereomeric excess was determined by ^{1}H NMR integration from the crude product mixture and then confirmed after chromatographic separation of the diastereomers. Along with the phenols **7**, **8**, **10**, **11**, a number of unidentified side-products were observed in this reaction. Based on the crude ^{1}H NMR spectrum, it could be concluded that most of them were products of alkyne oligomerization. However, side-products incorporating rings A and B of the carbene complexes were also formed, as judged by the presence of OMe signals in the crude ^{1}H NMR spectrum. The preparation of carbene complex **9** occurs with the formation of ~5–10% of the corresponding tetracarbonyl complex where the alkoxy group at C(7) is coordinated to the chromium.[11,12] Since carbene complexes **6** and **9**, and especially the tetracarbonyl complex of **9** are not very soluble in hexane, benzene was used as the solvent for these reactions. Unless otherwise specified, the benzannulation was run at 55–58 °C with 3-fold excess of alkyne (1 M in benzene).

The benzannulation reaction of carbene complexes **6a–f** with 1-pentyne afforded phenols **7a–f** in moderate to good yields (Table 1). We were pleased to observe high to complete diastereoselectivities in every case with benzene as solvent. Variations in the steric size of the R^1 substituents had no effect on the stereoselectivity of the reaction (entries 1–4): the only phenolic products isolated from the reactions of **6a–d** were



Scheme 2.

Table 1
Atropselective benzannulation reaction of carbene complexes **6** with alkynes[a]



6 **7** (a*R*,7*R*; a*S*,7*S*) **8** (a*R*,7*S*; a*S*,7*R*)

Entry	Solvent	Carbene complex	R^1	R^2	R_S	R_L	Product series	% Yield **7**+**8**[b]	dr (**7**:**8**)[c]
1	Benzene	**6a**	Me	Me	H	*n*-Pr	a	40	**7** Only
2	Benzene	**6b**	Et	Me	H	*n*-Pr	b	43	**7** Only
3	Benzene	**6c**	*i*-Pr	Me	H	*n*-Pr	c	47	**7** Only
4	Benzene	**6d**	*t*-Bu	Me	H	*n*-Pr	d	50	**7** Only
5	Benzene	**6e**	Me	Et	H	*n*-Pr	e	73	13.2:1
6	Benzene	**6f**	Me	*i*-Pr	H	*n*-Pr	f	72	12.5:1
7	Benzene	**6e**	Me	Et	H	TMS	g	45	**7** Only
8	Benzene	**6e**	Me	Et	H	Ph	h	39	**7** Only
9	Benzene	**6e**	Me	Et	H	*t*-Bu	i	43	**7** Only
10	Benzene	**6e**	Me	Et	Et	Et	j	58	**7** Only
11	$(CH_2Cl)_2$	**6a**	Me	Me	H	*n*-Pr	a	nd[d]	4.2:1
12	THF	**6a**	Me	Me	H	*n*-Pr	a	nd[d]	1.7:1
13	MeCN	**6a**	Me	Me	H	*n*-Pr	a	43	1:5.4
14	Benzene[e]	**6a**	Me	Me	H	*n*-Pr	a	nd[d]	5.3:1
15	Benzene[f]	**6a**	Me	Me	H	*n*-Pr	a	nd[d]	>20:1

[a] Unless otherwise specified, all reactions were carried out at 55–58 °C for 36 h with 3 equiv of alkyne at 0.33 M in carbene complex.
[b] Combined isolated yield of **7** and **8** after chromatography on silica gel. nd=not determined.
[c] Unless otherwise specified this is the ratio of isolated **7** and **8**.
[d] Ratio determined by ^{1}H NMR on crude reaction mixture.
[e] Reaction at 40 °C for 48 h.
[f] Reaction at 70 °C for 20 h.

identified as the (a*R*,7*R*; a*S*,7*S*) diastereomers **7a–d**. Diastereomer **8** couldn't be detected by NMR, HPLC, TLC even in the mixture of side-products. However, an increase in the size of the R^2 group on **6** led to a slight decrease in the stereoselectivity: from complete with **6a** (R=Me) to 12.5:1 with **6f** (R=*i*-Pr), all still favoring diastereomer **7** (entries 1, 5, and 6).

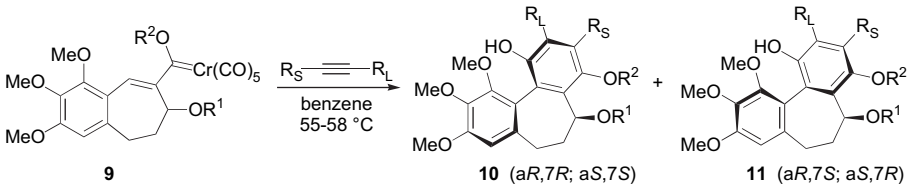
After probing the effects of substituent changes in the carbene complex **6** on the reaction with 1-pentyne, attention was then concentrated on defining the scope of the benzannulation in terms of the alkyne. Thus, the reaction of carbene complex **6e** with terminal alkynes, such as trimethylsilylacetylene, 3,3-dimethylbut-1-yne and phenylacetylene furnished allocolchicinoids **7g–i** in moderate yields (entries 7–9). The benzannulation with the internal alkyne 3-hexyne was also successful, giving the product **7j** (entry 10). Contrary to the reaction of **6e** with 1-pentyne, complete stereoselectivity for the (a*R*,7*R*; a*S*,7*S*) isomer **7** was observed in all four cases.

It was later noticed that a significant amount of the diastereomer **8** was formed in the reaction of **6a** with 1-pentyne in THF as a solvent. This prompted an undertaking of a solvent screening. Each reaction was performed with 20 mg of **6a** and, upon completion, the diastereoselectivity was determined by ^{1}H NMR as described above. Diastereomer **7** was favored in benzene and dichloroethane (entries 1 and 11). However, in THF both diastereomers formed in comparable amounts (entry 12) and in acetonitrile the opposite diastereomer **8** predominated (entry 13). Finally, the reaction was performed in benzene at different temperatures. A mixture of diastereomers was observed at 40 °C (entry 14), whereas only **7** was formed at 70 °C (entry 15). The preparative reaction in acetonitrile gave a moderate 43% yield with the preferential formation of diastereomer **8** (entry 13).

The benzannulation reaction of carbene complexes **9a–h** with 1-pentyne followed by oxidative demetalation in air afforded the benzannulated phenol products, each as a mixture of the (a*R*,7*R*; a*S*,7*S*) and (a*R*,7*S*; a*S*,7*R*) atropisomers **10** and **11**, respectively, with the diastereomer **11** as major in all cases (Table 2). The stereochemical assignments will be discussed below. In contrast to the reaction of complex **6**, the diastereoselectivity observed for complex **9** was only moderate, decreasing gradually with an increase in the steric size of both R^1 (entries 1–4) and R^2 groups (entries 1, 5, and 6). It recovers slightly only when both R^2 and R^1 are sterically demanding substituents (entry 7). The reaction of **9h** (R=MOM) (entry 8) showed the same diastereoselectivity as observed for **9a** (R=Me).

The benzannulation of carbene complexes **9a**,**c**,**d** with other terminal alkynes showed mixed results. The reaction of **9c** with trimethylsilylacetylene afforded the products **10i** and **11i** in moderate yield, but with lower selectivity for the (a*R*,7*S*; a*S*,7*R*) diastereomer than in the case of 1-pentyne (entry 9). Utilization of phenylacetylene in the benzannulation reaction with **9d** met with no success, giving only trace amounts of **10j** and **11j**, as judged from TLC and crude ^{1}H NMR

Table 2
Atropselective benzannulation reaction of carbene complexes **9** with alkynes[a]



9 **10** (a*R*,7*R*; a*S*,7*S*) **11** (a*R*,7*S*; a*S*,7*R*)

Entry	Carbene complex	R^1	R^2	R_S	R_L	Product series	% Yield **10**+**11**[b]	dr (**10**:**11**)[c]
1	**9a**	Me	Me	H	*n*-Pr	a	53	1:3.0
2	**9b**	Et	Me	H	*n*-Pr	b	45	1:2.4
3	**9c**	*i*-Pr	Me	H	*n*-Pr	c	51	1:2.4
4	**9d**	*t*-Bu	Me	H	*n*-Pr	d	48	1:2.0
5	**9e**	Me	Et	H	*n*-Pr	e	45	1:2.1
6	**9f**	Me	*i*-Pr	H	*n*-Pr	f	45	1:2.1
7	**9g**	*t*-Bu	*i*-Pr	H	*n*-Pr	g	48	1:3.4
8	**9h**	Me	MOM	H	*n*-Pr	h	39	1:3.0
9	**9c**	*i*-Pr	Me	H	TMS	i	51	1:1.3
10	**9d**	*t*-Bu	Me	H	Ph	j	<10	nd
11	**9a**	Me	Me	H	*t*-Bu	k	32	1:7.0[d]
12	**9a**	Me	Me	Et	Et	l	<10	nd
13	**9a**	Me	Me	H	*n*-Pr	a	nd	1:2.9[e,f]

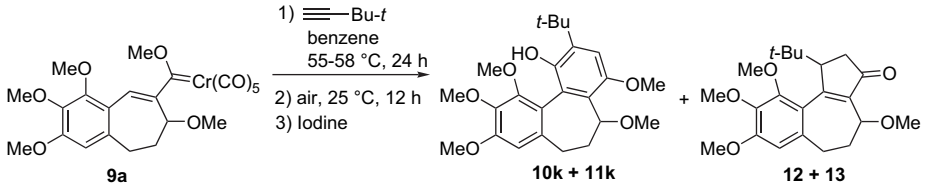
[a] Unless otherwise specified, all reactions were carried out at 55–58 °C for 24 h with 3 equiv of alkyne at 0.33 M in carbene complex.
[b] Combined isolated yield of **10** and **11** after chromatography on silica gel. nd=not determined.
[c] Unless otherwise specified this is the ratio of isolated **10** and **11**.
[d] This reaction also produced a 9% yield of **12** and a 20% yield of **13**.
[e] Ratio determined by ^{1}H NMR on crude reaction mixture.
[f] Reaction in THF.

spectroscopy (entry 10). Extensive polymerization of the alkyne was observed in this case.

Carbene complex **9a** reacted with 3,3-dimethylbut-1-yne to furnish the expected phenols **10k** and **11k**, which were formed in higher diastereoselectivity than was observed with 1-pentyne (entry 11, Scheme 3). Significant amounts of diastereomeric cyclopentenone products **12** and **13** were observed in this reaction. These five-membered ring annulated products result from cyclization without CO insertion, followed by hydrolysis of the cyclopentadiene product. This was surprising, since the formation of the five-membered ring products is rarely observed in the benzannulation reaction of vinyl carbene complexes of chromium.[13] It was reasoned that performing this transformation under an atmosphere of CO would affect the phenol/cyclopentenone ratio in favor of the phenol product. However, the product distribution was only slightly affected by this modification (Scheme 3). Attempts to use the internal alkyne, 3-hexyne, in this benzannulation reaction have been so far unsuccessful, only trace amounts of phenol products were formed from this acetylene and carbene **9a**, as estimated from TLC and crude ^{1}H NMR (Table 2, entry 12).

Contrary to carbene complex **6a**, the benzannulation reaction of **9a** with 1-pentyne in THF showed almost the same diastereoselectivity as observed in benzene (Table 2, entry 13).

Assignment of the relative stereochemistry of pairs of atropisomers of **7** and **8** and **10** and **11** was made on the basis of their ^{1}H NMR spectra and confirmed by X-ray diffraction for **11a**.[9] In the (a*R*,7*S*; a*S*,7*R*) diastereomer where the C(7) functionality is in a pseudoaxial position, the dihedral angle between C(7)–H and C(6)–Ha is about 90° resulting in the absence of coupling between these protons (Fig. 1). The dihedral angle between C(7)–H and C(6)–Hb is about 30° and the C(7)–H signal appears as a doublet in ^{1}H NMR spectrum. On the other hand, the (a*R*,7*R*; a*S*,7*S*) diastereomer has its C(7) functionality in a pseudoequatorial position with the dihedral angles between C(7)–H and C(6)–Ha and C(6)–Hb close



9a **10k + 11k** **12 + 13**

conditions	% Yield **10k + 11k**	dr **10k : 11k**	% Yield **12 + 13**	dr **12 : 13**
under Ar	32	1 : 7	29	1 : 2.0
under CO	39	1 : 7	21	1 : 2.3

Scheme 3.

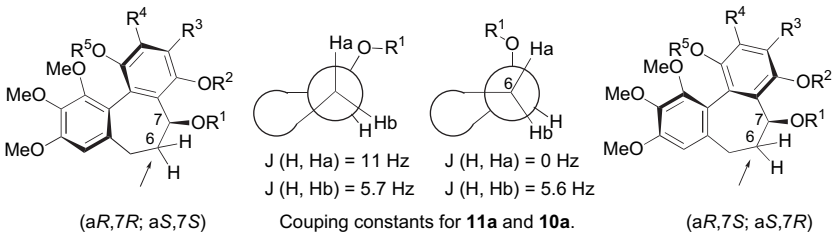


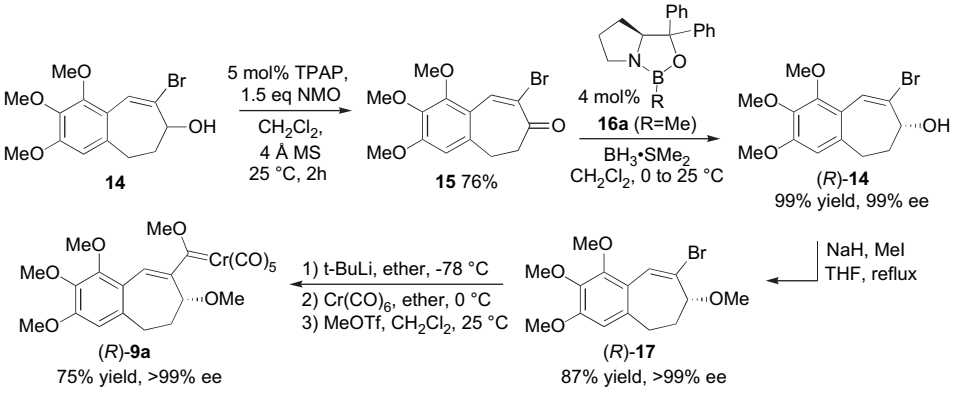
Figure 1. Determination of relative configuration of the diastereomers.

to 150 and 30°, respectively. In this case, a doublet of doublets for C(7)–H is observed in the ^{1}H NMR spectrum. The coupling constants given in Figure 1 are for compounds **11a** and **10a** and as predicted from the model, the C(7)–H signal in the (a*R*,7*S*; a*S*,7*R*) diastereomer of **11a** appears in ^{1}H NMR spectrum as doublet with J=5.6 Hz. The same proton of the (a*R*,7*R*; a*S*,7*S*) diastereomer **10a** shows a doublet of doublets with J=5.7 and 11 Hz. The other derivatives of **10** and **11** and of **7** and **8** also follow this trend.

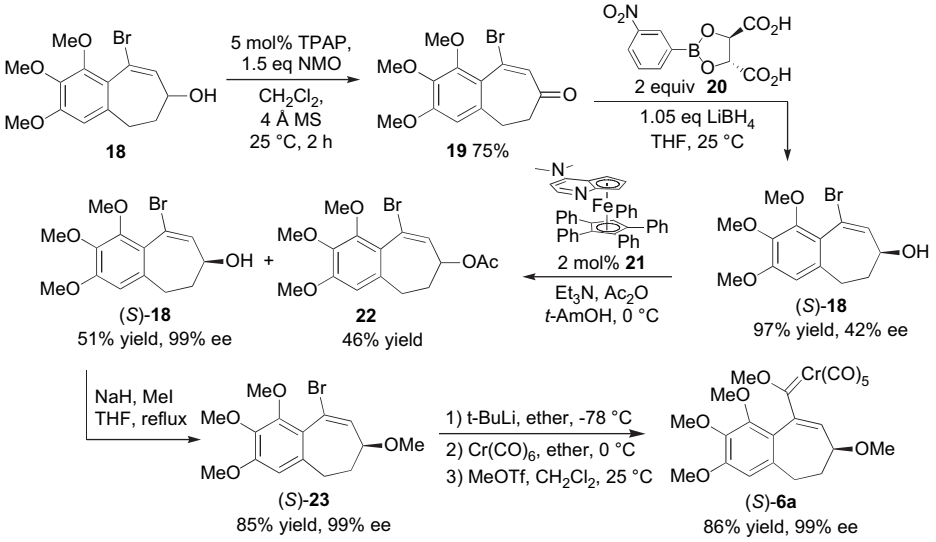
To access the enantiomerically enriched configurationally stable allocolchicinoids, it was necessary to develop efficient methodology for the asymmetric synthesis of carbene complexes **9** and **6.** The key enantiogenic step in each synthesis is the asymmetric reduction of the ketones **15** and **19**, respectively (Schemes 4 and 5). The syntheses begin with the oxidation of the previously reported alcohols **14**[14] and **18**[9] to the ketones **15** and **19**, which were performed under the standard conditions[15] reported for oxidation with *N*-methylmorpholine-*N*-oxide (NMO) catalyzed by 5% tetrapropylammonium perruthenate (TPAP) (Schemes 4 and 5). Both reactions proceeded similarly, giving **15** and **19** in good yield. However, we were unable to drive the reactions to completion, about 15% of the unreacted starting material was observed in each case. Performing the reactions in CH_3CN instead of CH_2Cl_2 or the use of increased amounts of TPAP failed to improve the conversion of the starting material. Fortunately, unreacted alcohols **14** and **18** can be readily chromatographically separated from **15** and **19** and recycled.

Asymmetric reduction of ketones **15** and **19** was initially examined using the catalytic CBS protocol.[16] The commercially available oxazaborolidine (*S*)-**16a** (R=Me) and its Me_3SiCH_2 analog **16b**, prepared according to literature procedure,[17] were examined in both catalytic and stoichiometric amounts (Table 4, Section 4). The enantiomeric purity of the resulting alcohols **14** and **18** was determined by HPLC. Thus, reduction of ketone **15** by BH_3–SMe_2 in CH_2Cl_2 at 0 °C in the presence of either catalytic or equimolar amounts of the oxazaborolidines (*S*)-**16a** or (*S*)-**16b** readily afforded the alcohol (*R*)-**14** in high chemical and optical yields. Under the optimized conditions (*R*)-**14** was prepared in 99% chemical and 99% optical yields. In contrast to **15**, the stereoselectivity observed in the reduction of ketone **19** to give (*R*)-**18** was low, even when stoichiometric amounts of (*S*)-**16a** were used (Table 4, Section 4). The use of the bulkier B–CH_2TMS oxazaborolidine (*S*)-**16b** was expected to improve the situation by the steric interaction of the CH_2TMS group with the β-Br in **19**, however, no enhancement in enantiomeric purity of the resulting alcohol (*R*)-**18** was observed.

The low enantioselectivity observed in the CBS reduction of ketone **19** prompted the search for another approach to the stereoselective preparation of alcohol (*S*)-**18**. Chiral Lewis acid TarB–NO_2 **20**, prepared from the corresponding arylboronic and (+)-tartaric acids, has been previously shown to induce high enantioselectivity in the asymmetric reduction of ketones by $LiBH_4$ to the corresponding secondary alcohols.[18] Unfortunately, **20** cannot be used catalytically and for the best results the reaction requires 2 equiv of TarB–NO_2. However, after the reaction is complete, the relatively expensive arylboronic acid can be recovered and reused. Reduction of ketone **19** using the above described conditions afforded the alcohol (*S*)-**18** in excellent yield and 42% ee (Scheme 5). It is worth noting that this reduction gives (*S*)-**18** as the major



Scheme 4.



Scheme 5.

enantiomer, whereas (*R*)-**18** was the major isomer obtained by CBS reduction with (*S*)-**16a**.

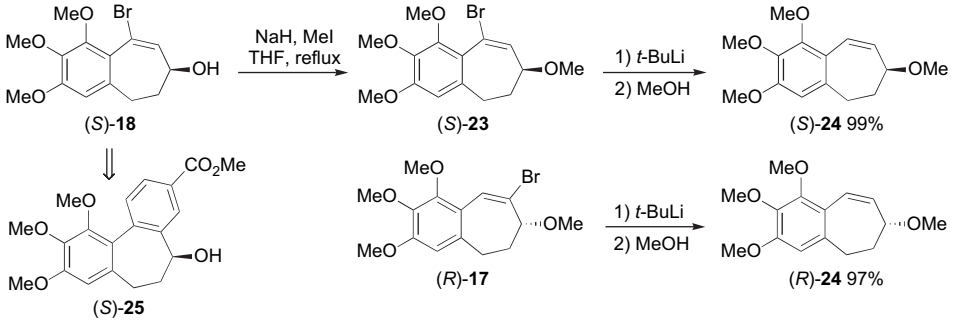
An alternative approach toward the enantiomerically enriched alcohol (*S*)-**18** would be kinetic resolution of racemic **18**. Apart from enzymatic methods, kinetic resolution of alcohols can be accomplished through acylation or oxidation. Thus, recently developed conditions[19] for palladium-catalyzed oxidative kinetic resolution of alcohols in the presence of (−)-sparteine were applied to **18**. Unfortunately, no reaction was observed even after the prolonged (92 h) exposure of an 80 °C solution of **18** in toluene to oxygen atmosphere.

Kinetic resolution of **18** through acetylation catalyzed by planar chiral DMAP analog (−)-**21**[20] was more successful (Scheme 5). Promising selectivity[21] (s=13.2) was observed in the kinetic resolution of (*S*)-**18** (42% ee) with a newly opened bottle of catalyst (−)-**21**. The slower reacting enantiomer in this kinetic resolution was (*S*)-**18**. To our disappointment, the selectivity gradually decreased in consecutive runs with the same batch of (−)-**21** to a value of $s\sim5.5$. This same level of selectivity ($s\sim5.5$) was also observed when recycled catalyst was utilized. Such behavior of this catalyst is surprising, since it should not be affected by oxygen and moisture present in the air. Indeed, when the catalyst was stored and used under argon, comparable results were obtained ($s\sim5.5$). Although the selectivity observed in this kinetic resolution was not synthetically useful for resolving the racemate of **18**, it was useful for enhancement of the enantiomeric purity of (*S*)-**18** that was obtained from the asymmetric reduction of **19** in the presence of the chiral Lewis acid **20** (Scheme 5). It was found that (*S*)-**18** of 42% ee could be improved to 99% enantiomeric purity at 49% conversion, which corresponds to a selectivity $s>13$.[22]

Methylation of the enantiomerically enriched alcohols (*S*)-**18** and (*R*)-**14** was performed under the standard conditions to give the corresponding methylated substrates (*S*)-**23** and (*R*)-**17**, respectively, both in good yields and both of which were found by HPLC to be of the same optical purity as the starting alcohols (Schemes 4 and 5). Enantiomerically enriched carbene complexes were subsequently prepared from (*S*)-**23** and (*R*)-**17** using the conditions previously developed for the synthesis of the corresponding racemic carbene complexes. The preparation of (*S*)-**6a** and (*R*)-**9a** was accomplished without loss of enantiomeric purity (HPLC). These carbene complexes did not racemize even when left overnight on a silica gel column or when their solution in CH_2Cl_2 was treated with acetic acid. However, when (*S*)-**6a** was stirred with NEt_3 in CH_2Cl_2 for 11 h, its enantiomeric purity decreased to 94% ee. Under the same conditions racemization of carbene complex (*R*)-**9a** was not detected.

The absolute stereochemistry assignments of the alcohols (*R*)-**14** and (*S*)-**18** were made by the chemical correlation shown in Scheme 6. We have recently reported[6b] the conversion of alcohol (*R*)-**25** to natural (−)-(7*S*)-allocolchicine **1**, which relied on the following sequence: (±)-**18** to (±)-**25** to (*R*)-**25** to (−)-(7*S*)-**1**. Comparison of (*S*)-**25**, prepared from (*S*)-**18**, with (*R*)-**25** used in the synthesis of allocolchicine **1** revealed that these were opposite enantiomers, therefore confirming the stereochemical assignment in (*S*)-**18**. The following steps were taken to secure the absolute configuration in the regioisomeric vinyl halide (*R*)-**14**. Bromine was removed from both the methyl ethers (*S*)-**23** and (*R*)-**17** by treatment with *t*-BuLi followed by protonation, giving alkene **24** in almost quantitative yield. Although it was not possible to measure the enantiomeric excess of **24** by HPLC, it was assumed that the reaction occurred with full retention of C(7) stereochemistry, since no racemization was observed during the preparation of the carbene complexes (*S*)-**6a** and (*R*)-**9a**. The products **24** obtained from (*S*)-**23** and (*R*)-**17** were compared and found to be in an enantiomeric relationship with identical but opposite optical rotations.

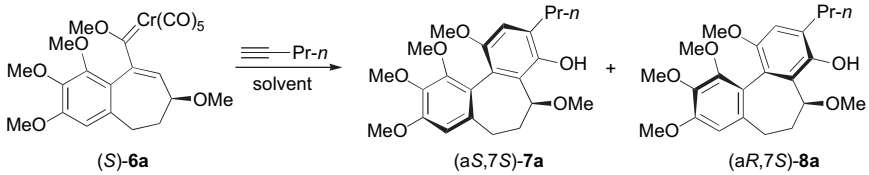
Reaction of carbene complex (*S*)-**6a** with 1-pentyne was carried out under the conditions developed for the benzannulation reaction of racemic complex **6a** (Table 1). As expected, the reaction afforded the phenol (a*S*,7*S*)-**7a**. We were quite surprised to find out that the enantiomeric purity of this



Scheme 6.

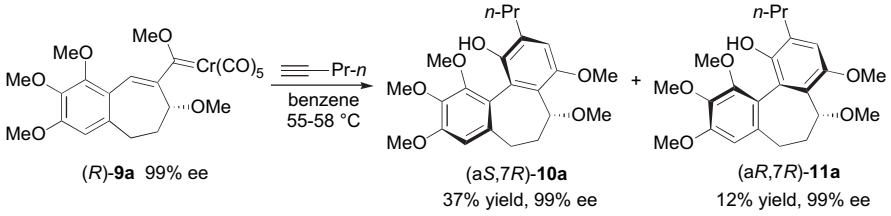
material was only 72% ee, which indicated that partial racemization occurred in the course of the benzannulation reaction (entry 1). A possible explanation for this racemization is presented below. Traces of the minor (a*R*,7*S*) diastereomer **8a** were observed in the reaction mixture, which was contrary to the results obtained in the benzannulation reaction of racemic **6a** (Table 1). The following experiments were performed with small amounts of enantiomerically enriched (*S*)-**6a** (99% ee) to find the best conditions for the benzannulation reaction (Table 3, entries 2–13). Thus, the reaction was performed in benzene with a 3-fold excess of 1-pentyne at 58 °C (standard conditions) to afford **7a** and **8a** with a diastereomeric ratio of 9.8:1 as determined by ^{1}H NMR integration (entry 2). The enantiomeric excess of diastereomers **7a** and **8a** was assessed by HPLC and found to be 80 and 99% ee, respectively, showing that only diastereomer **7a** was formed with a decrease in optical purity. Increase in the reaction temperature clearly led to a decrease in the enantiomeric excess of (a*S*,7*S*)-**7a** (entries 2, 3, and 4). The effect of concentration was not so pronounced, since running the reaction 5-fold diluted gave the product with similar ee (entries 2 and 5). The use of several other solvents in this reaction was evaluated (entries 6–10). Of the solvents examined, only in neat 1-pentyne was the loss of optical purity completely prevented (entry 6). In THF the enantiomeric excess of **7a** was not eroded as much as it was in benzene, but in this solvent the diastereomer (a*R*,7*S*)-**8a** was also formed in significant amounts (entry 10). Since it is not practical to run the benzannulation reaction in neat alkyne, THF was employed as the solvent in further optimization experiments. The enantiomeric excess of the diastereomer **7a** sharply decreased and that of **8a** remained unchanged with an increase in the reaction temperature (entries 10–12). Running the reaction at higher temperature helps improve the diastereomeric ratio in favor of isomer **7a**. Dilution of the

Table 3
Benzannulation reaction of chiral nonracemic carbene complexes (*S*)-**6a**[a]



Entry	Solvent	[**6a**] (M)	Temp (°C)	Time (h)	% Yield	dr (**7**:**8**)[b]	% ee **7**[c]	% ee **8**[c]
1	Benzene	0.33	58	36	46[d]	nd	72	nd
2	Benzene	0.33	58	36	nd	9.8:1	80	99
3	Benzene	0.33	85	12	nd	nd	54	nd
4	Benzene	0.33	40	48	nd	nd	93	nd
5	Benzene	0.066	58	36	nd	nd	79	nd
6	1-Pentyne	0.33	58	13	nd	nd	99	nd
7	*n*-Heptane	0.33	58	36	nd	nd	60	nd
8	CH_2Cl_2	0.33	58	36	nd	nd	58	nd
9	MeCN	0.33	58	36	nd	1:5.7	82	99
10	THF	0.33	58	36	nd	1.4:1	90	99
11	THF	0.33	70	20	nd	>20:1	16	99
12	THF	0.33	85	14	nd	>20:1	8	99
13	THF	0.033	58	36	nd	1.1:1	94	99
14	THF	0.33	35	60	85[e]	2.7:1	99	99

[a] Unless otherwise specified, all reactions were carried out at 55–58 °C for 36 h with 3 equiv of alkyne at 0.33 M in carbene complex. nd=not determined.
[b] Ratio determined by ^{1}H NMR on crude reaction mixture.
[c] Determined after chromatographic separation of **7** and **8** by HPLC with a Chiralcel OD-H column.
[d] Isolated yield of **7** after chromatography on silica gel.
[e] Combined isolated yield of **7** and **8** after chromatography on silica gel.



(*R*)-**9a** 99% ee

(a*S*,7*R*)-**10a**
37% yield, 99% ee

(a*R*,7*R*)-**11a**
12% yield, 99% ee

Scheme 7.

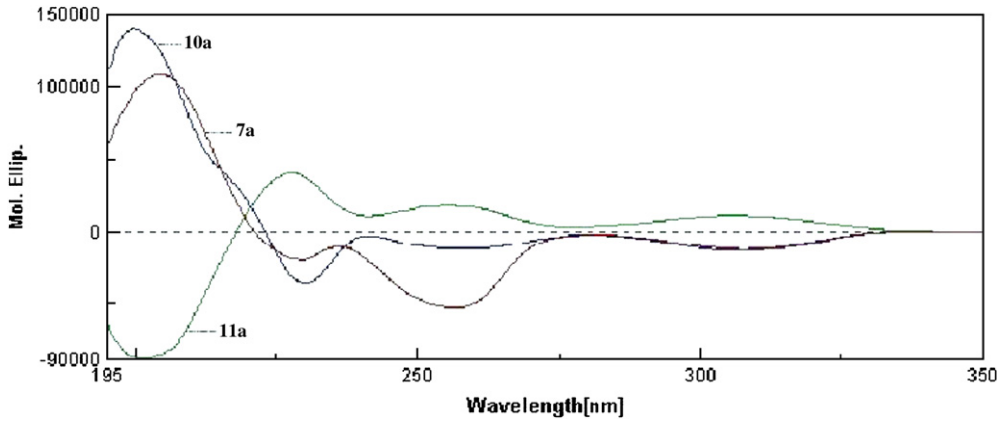


Figure 2. CD spectra of **10a**, **7a**, and **11a**.

reaction mixture was found to have only little effect on the enantioselectivity, but led to the formation of almost equimolar amounts of diastereomers **7a** and **8a** (entries 10 and 13). Based on our findings, the reaction of (*S*)-**6a** with 1-pentyne was carried out in THF at the lowest possible temperature (35 °C) to avoid the loss of optical purity. Indeed, diastereomers (a*R*,7*S*)-**8a** and (a*S*,7*S*)-**7a** were formed under these conditions in a 1:2.7 ratio, both in 99% ee (entry 14). It is worth noting that the yield in this reaction was much higher than using benzene as a solvent (entries 1 and 14).

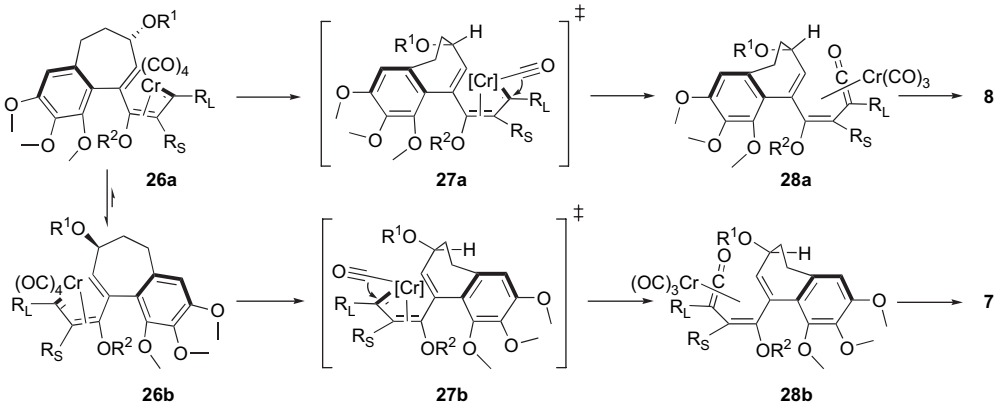
Reaction of the carbene complex (*R*)-**9a** with 1-pentyne was performed under the conditions developed for the benzannulation reaction of the corresponding racemic carbene complex (Scheme 7). This reaction gave the two diastereomeric phenols (a*S*,7*R*)-**10a** and (a*R*,7*R*)-**11a** in a 3:1 ratio, which was in line with the racemic complex. The enantiomeric excess of the products was determined by HPLC and found to be more than 99% ee for both of the diastereomers.

The absolute configuration in (a*S*,7*S*) diastereomer **7a**, the (a*S*,7*R*) diastereomers **10a**, and the (a*R*,7*R*) diastereomer **11a** has been tentatively assigned based on their CD spectra by comparison with the CD spectra of similarly substituted biaryls[23] (Fig. 2). Thus, phenols **7a** and **10a** exhibited negative Cotton effect (CE) at 229 and 230 nm and positive CE at 205 and 200 nm, respectively, suggesting an a*S* axial configuration for these compounds. On the contrary, phenol **10a** showed positive CE at 228 nm and negative CE at 201 nm, as expected for an a*R* axial configuration. Consequently, 7*S* configuration was assigned to the series of enantiomerically enriched compounds **18**, **6a**, **7a**, and **8a** and the opposite 7*R* configuration—to the series **14**, **9a**, **10a**, and **11a**.

2.1. Mechanism and discussion

The asymmetric induction observed in the formation of the diastereomers **7** and **8** and **10** and **11** probably occurs via the face-selective installation of a chromium tricarbonyl group in one of the reaction intermediates, which leads to overall central-to-planar-to-axial chirality transfer. To support this hypothesis, the isolation and structural elucidation of an air-stable protected phenol chromium tricarbonyl complex would be highly desirable. Unfortunately, all our attempts to trap the intermediate chromium tricarbonyl complexes of the phenols produced in the reaction of carbene complex **6a** with 1-pentyne by triflation or methylation met with no success.

To account for the observed diastereoselectivity in the benzannulation reactions of carbene complexes **6** the following model is proposed (Scheme 8).[24,25] Due to the high barrier to the rotation about the biaryl bond,[10] the atropisomers **7** and **8** cannot equilibrate under the reaction conditions, nor would it be expected for their corresponding chromium tricarbonyl complexes. Thus, the stereochemistry must be determined prior to the cyclization of either the vinyl ketene complex **28a** or **28b**. It is also assumed that the ketene complexes **28a** and **28b** do not interconvert since DFT calculations reveal that the vinyl ketene generated from alkenyl carbene complexes does not have a local minimum but rather that CO insertion and electrocyclic ring closure are a single step.[25] This is consistent with the fact that the vinyl ketene complex cannot be intercepted even if the benzannulation reaction is performed in methanol as solvent.[26] Thus the likely transition states are **27a** and **27b** that result when CO migration from chromium to carbon occurs in the diastereomeric η^1,η^3-vinyl carbene complexes **26a** and **26b**.

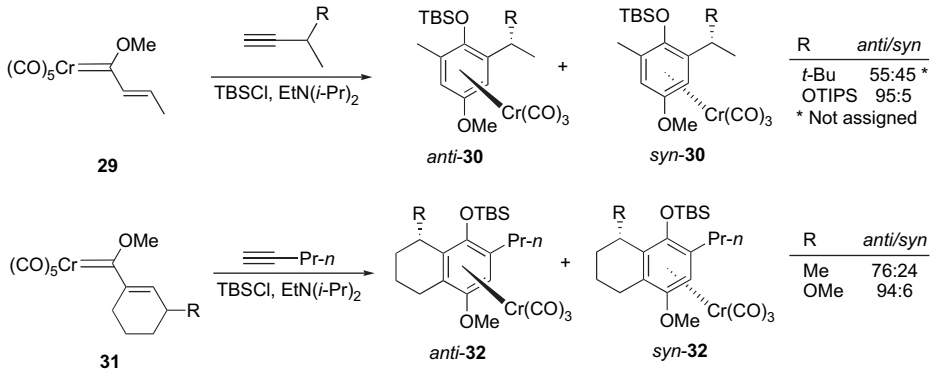


Scheme 8.

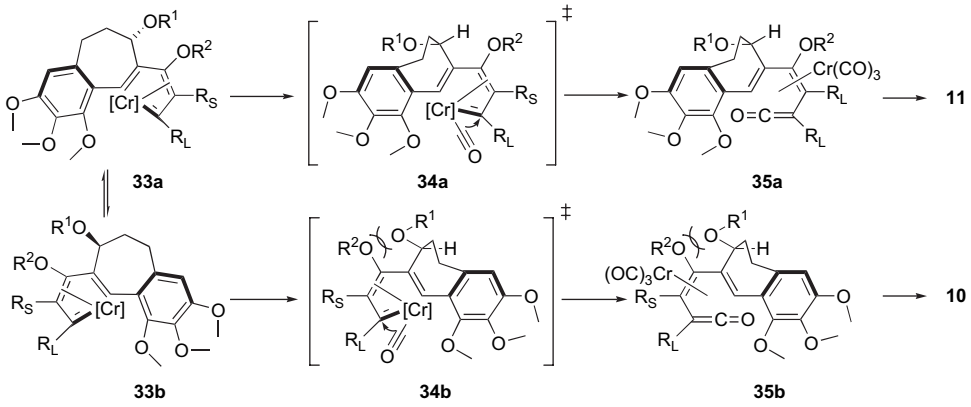
The key assumption is that the reaction of carbene complex **6** and an alkyne kinetically affords the η^1,η^3-vinyl carbene intermediate **26a** which results from the addition of the alkyne to the carbene complex **6** where the chromium is above the plane of the molecule and the alkoxy group is below. Support for this assumption can be taken from the reaction of alkenyl carbene complexes with propargyl ethers (Scheme 9). The reaction of complex **29** with the TIPS ether of 3-butyn-1-ol gives a 95:5 mixture of the arene chromium tricarbonyl groups **30** shown in Scheme 9 with the *anti*-isomer predominating.[27] The size and electronic nature of the protecting group on the oxygen both contributed to the high selectivity. The origin of the stereoselectivity was attributed to a stereoelectronic effect in which the propargylic oxygen substituent has a conformational preference to be *anti* to the chromium in the η^1,η^3-vinyl carbene complexed intermediate. In a more closely related example, the reaction of carbene complex **31** with 1-pentyne gives rise to the arene chromium tricarbonyl complexes **32** in which the *anti*-isomer predominates by a factor of 96:4 when R is methoxyl and only 76:24 when R is methyl.[28] The origin of this selectivity may again be due to a stereoelectronic preference for the methoxyl group to be *anti* to the chromium in the η^1,η^3-vinyl carbene complexed intermediate.

With the assumption that **26a** is the kinetic η^1,η^3-vinyl carbene complexed intermediate, it can be seen that CO insertion and cyclization in **26a** would lead to the diastereomer **8**, which is not the major product of the reaction of carbene complex **6** and 1-pentyne (Scheme 8). The major product is the diastereomer **7** which would come from CO insertion in the η^1,η^3-vinyl carbene complexed intermediate **26b**. The conversion of **26a** to **26b** requires inversion of both the planar and axial configurations. The latter involves rotation about a single bond, which is controlled by the steric interaction of OR^2 and OMe substituents and is expected to proceed but with a significant barrier. In order to explain the results observed here, the η^1,η^3-vinyl carbene complexed intermediate **26a** must be able to isomerize to **26b** and thus the η^1,η^3-vinyl carbene complexed intermediate **26b** must be more stable than **26a** (or perhaps more reactive). Of the two, intermediate **26a** is the diastereomer with the OR^1 functionality in a pseudoaxial position on ring B and the $Cr(CO)_4$ fragment *anti* to the methoxy substituents on ring A. Intermediate **26b** has its OR^1 group in a pseudoequatorial position and on this basis may be expected to be more thermodynamically favorable.

Both of the η^1,η^3-vinyl carbene complexed intermediates **26a** and **26b** can undergo CO insertion to give ketene complexes **28a** and **28b** via transition states **27a** and **27b**, respectively. If the conversion of **26a** to **26b** is slow relative to the CO insertion, then **26a** will react via transition state **27a** to form **28a**, which will undergo cyclization followed by demetalation to afford phenol **8**. However, if conversion of **26a** to **26b** is complete before CO insertion can occur, then exclusive formation of the diastereomer **7** would result via vinyl ketene complex **28b**. Thus the branchpoint for product formation



Scheme 9.

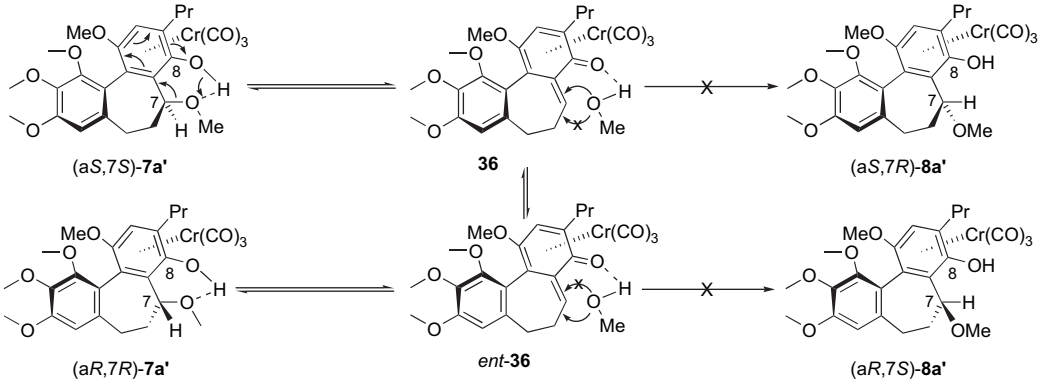


Scheme 10.

would be the η^1,η^3-vinyl carbene complexed intermediate **26a** and the ratio of **7** to **8** would be expected to be a function of the relative rates of CO insertion to give **28a** and of isomerization to the η^1,η^3-vinyl ketene complexed intermediate **26b**. This situation is probably realized in the reaction of **6a** with 1-pentyne in benzene. For **6e**,**f** with a bulkier R^2 group, the barrier to the rotation in **26a** increases, thus slowing down the conversion to **26b**, which results in the formation of some **28a**, and, consequently, minor diastereomer **8** (Table 1, entries 6 and 7). Diastereomer **8** disappears if the reaction is performed at higher temperature, suggesting a higher rate of conversion of **26a** to **26b** (Table 1, entries 14 and 15). Polar coordinating solvents would be expected to stabilize the transition states **27** by coordination to the chromium center during CO insertion, hence accelerating the reaction, which will lead to increased formation of ketene complex **28a** and the product ratio will be biased toward diastereomer **8**. Indeed, if the reaction of **6a** with pent-1-yne is run in THF or CH_3CN, increased amounts of diastereomer **8** are observed (Table 1, entries 12 and 13).

A similar situation can be considered in the benzannulation reaction of carbene complexes **9**. In this case, however, the interconversion of the diastereomeric vinyl carbene intermediates **33a** and **33b** is expected to be fast, due to the absence of the OR^2–OMe steric interaction (Scheme 10). The selective kinetic formation of **33a** would not be expected in this case since the alkoxy group is cross-conjugated to the η^1,η^3-vinyl carbene complexed intermediate **33** just as it is in the starting carbene complex **9a**. Given the different position of the carbene complex on the seven-membered ring, close contacts of interest in this case may involve the steric interaction between OR^2 and OR^1 groups, which may be expected to disfavor the transition state **34b** relative to **34a** and thus to the preferential formation of the phenol **11** as the major product as is in fact seen to be the case (Table 2). Surprisingly, the diastereomeric ratio only poorly correlates with the size of R^2 and R^1 substituents, but is found in all cases to be between 2.1:1 and 3.4:1. The reason that the nature of the acetylene has such a pronounced effect not only on the diastereomer distribution (Table 2, entry 11) but also on the product distribution (Table 2, entries 10–12) is not completely clear at this time.

In the benzannulation reaction of optically pure carbene complex (*S*)-**6a** with 1-pentyne, the phenolic product (a*S*,7*S*)-**7a**, but not its diastereomer (a*R*,7*S*)-**8a**, showed decreased enantiomeric purity (Table 3). This was completely unexpected, since this racemization would require an inversion of both the central and axial chiral elements. It cannot be explained by racemization of the carbene complex since only one of the diastereomers is racemized. Thus, the racemization must occur after the stereochemistry of each diastereomer **7** and **8** is set and the inversion of the central chiral element at C(7) would most likely involve a dissociation of the C(7)–O



Scheme 11.

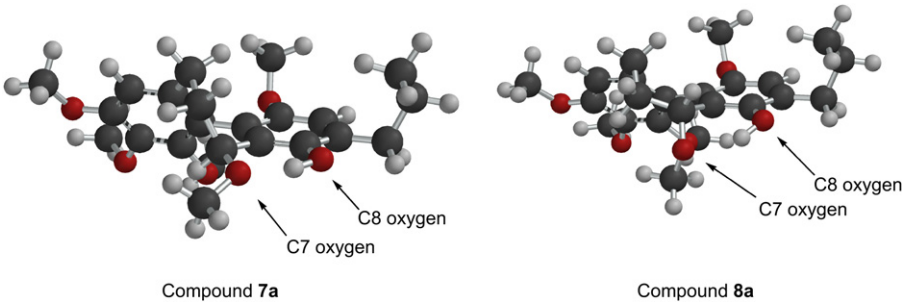


Figure 3. Minimized structures of diastereomers **7a** and **8a**.

bond. To provide an explanation for these observations, we propose that intramolecular hydrogen bonding[10] between C(8)–OH and pseudoequatorial C(7)–OMe occurs in chromium tricarbonyl complex (a*S*,7*S*)-**7a′**, but not in (a*R*,7*S*)-**8a′**, where the C(7)–OMe group is in pseudoaxial position (Scheme 11). The compound (a*S*,7*S*)-**7a′** is the chromium tricarbonyl complex of phenol **7a** where the stereochemistry of the chromium tricarbonyl group is assigned based on the reaction of complex **31** (R=OMe) shown in Scheme 9. To support the idea that intramolecular hydrogen bonding is more important in **7a′** than in **8a′**, these compounds were energy minimized (without the $Cr(CO)_3$ group) with the molecular mechanics routine in Spartan 04 and the two resulting structures are shown in Figure 3. The two oxygens on carbons 7 and 8 are nearly in the same plane containing the benzene ring formed in the benzannulation for **7a** but in **8a** the oxygen on carbon 7 is considerably below this plane. The O–O distance is 2.52 Å for **7a** and 2.84 Å for **8a**. The hydrogen on the oxygen at the C8 position in both structures is pointing directly at the oxygen at the C7 position and the resulting H–O distance is 2.00 Å for **8a** and 1.62 Å for **7a**.

The key to the proposal for the epimerization of **7a′** outlined in Scheme 11 is that the presence of the $Cr(CO)_3$ moiety and the intramolecular hydrogen bond assist the reversible dissociation of methanol in (a*S*,7*S*)-**7a′** to give the *o*-quinone methide chromium tricarbonyl complex **36**. Because the intramolecular H-bonding is only possible in diastereomer **7**, the opposite diastereomer **8** will not participate in this reaction and its enantiomeric purity will remain unchanged. The re-addition of methanol to **36** will be assisted by H-bonding to the carbonyl group and will follow the same pathway, giving the starting material (a*S*,7*S*)-**7a′**. However, if axial inversion in **36** to afford *ent*-**36** is relatively fast, addition of methanol to *ent*-**36** will furnish (a*R*,7*R*)-**7a′**, which is the enantiomer of the starting material. Although the barrier to the rotation in **7a** and, likely, in **7a′** is high and will not allow the axial inversion under the reaction conditions,[10] it may be lower in the *o*-quinone methide complex **36** due to the loss of aromaticity of ring C and the installation of a double bond in ring B. Presumably, both H-bonding and $Cr(CO)_3$ coordination are necessary elements for this reaction to occur, since less racemization is observed when polar coordinating solvents are used in the benzannulation reaction, which can be best explained by early displacement of $Cr(CO)_3$ from (a*S*,7*S*)-**7a′**, hence stopping the racemization pathway.

The formation of *o*-quinone methide intermediates related to **36** has been previously postulated in the benzannulation reaction of aryl and heteroaryl carbene complexes with alkynes.[29] Following the benzannulation reaction, elimination of the benzylic oxygen functionality generates *o*-quinone methide and alkene intermediates, which subsequently participated in a hetero-Diels–Alder reaction to form the isolable dimeric products.[29a,b] In our case, incorporation of C(7)–OCD_3 group in **7a** would be expected if the benzannulation reaction was carried out in the presence of CD_3OD, which would support the proposed racemization pathway. Thus, performing the reaction of (*S*)-**6a**, 10-fold excess of CD_3OD, and 1-pentyne under the conditions of entry 12, Table 3 resulted in a significantly different diastereomeric ratio (**7a**:**8a**=1.6:1) and enantiomeric excess of **7a** (87% ee). The latter observation indicated that the additive inhibited the racemization pathway, probably by the displacement of $Cr(CO)_3$ from **7a′**. Incorporation of OCD_3 group at C(7) of **7a** was investigated by mass spectrometry and found to be low ($\leq$10%). Similar inhibition of racemization by CD_3OD (90% ee of **7a**) was also observed when the reaction was run in benzene according to the conditions of entry 3 of Table 3. Further studies aimed to support the proposed racemization mechanism are underway.

3. Conclusion

The benzannulation of α,β-unsaturated carbene complexes with alkynes provides moderate to good yields of allocolchicinoids with moderate to high diastereoselectivities. The stereoselectivity results from the creation of an axial chiral element of a biaryl bond when the new benzene ring is formed via a stereo-relay from an alkoxy group at a chiral center that will become the C(7) carbon in the product. The stereoselectivity is high when the alkenyl carbene complex is in conjugation with the alkoxy group and much lower when the alkoxy group is cross-conjugated with the carbene complex. This is proposed to result from the kinetic formation of an η^1,η^3-vinyl carbene complexed intermediate that is less stable than its diastereomer. With increased temperature, isomerization occurs to give the more stable diastereomer of this intermediate and the formation of a single diastereomer of the product. The reaction of optically pure carbene complexes with alkynes can occur to either give complete retention of the stereochemistry of the alkoxy group in the carbene complex or racemization. The racemization was found to occur after the product was

formed and not in the starting carbene complex. One of the diastereomers of the product can be racemized but not the other. This was proposed to be a result of the generation of an *o*-quinone methide chromium tricarbonyl intermediate whose formation is made possible by an intramolecular hydrogen bond that is conformationally possible in one diastereomer of the product but not in the other.

4. Experimental

4.1. General information

Routine NMR spectra were recorded on 300, 400, 500, and 600 MHz Bruker and Varian instruments in $CDCl_3$ (internal standard tetramethylsilane, δ_H, δ_C=0.00 ppm), benzene-d_6 (δ_H=7.15 ppm, δ_C=128.0 ppm), acetone-d_6 (δ_H=2.04 ppm, δ_C=29.8 ppm), DMSO-d_6 (δ_H=2.49 ppm, δ_C=39.5 ppm). Proton signal assignments in the ^{1}H NMR spectra, which where not obvious from the chemical shift and multiplicity data, were determined using standard COSY and NOESY experiments. Carbon signal multiplicities in the ^{13}C NMR spectra were determined from standard DEPT experiments. Mass spectral analyses (low and high resolutions) were performed at both Michigan State University and University of Zürich Mass Spectrometry Facilities. Elemental analyses were performed by Galbraith Laboratories, Inc, Knoxville, TN. Anhydrous ether and THF were distilled under nitrogen from sodium benzophenone ketyl. Anhydrous benzene and toluene were distilled under nitrogen from sodium. Anhydrous methylene chloride was distilled under nitrogen from CaH_2. Unless otherwise mentioned, all reagents were purchased from commercial sources and were used without further purification. Isolated yields are reported for compounds estimated to be more than 95% pure as determined by ^{1}H NMR or combustion analysis. In the cases where the product ratios were determined from the crude mixture by integration of their ^{1}H NMR signals, the spectra were obtained from the solutions containing at least 30 mg of the mixture in 0.6 mL of $CDCl_3$ with at least 16 scans.

4.2. General procedure for the benzannulation reaction of carbene complexes **6** with alkynes

The following procedure is related to one reported for the reaction of complexes **6** with 1-pentyne.[9] An approximately 0.33 M solution of the appropriate carbene complex **6** in the requisite solvent was introduced into a single necked pear shaped flask in which the 14/20 joint was replaced with a threaded high-vacuum Teflon stopcock. A 3-fold excess of the desired alkyne was added and the resulting solution was deoxygenated by the freeze–pump–thaw method (−196 °C/25 °C, three cycles). The flask was back-filled with argon at room temperature, sealed and then heated for 36 h at 55–58 °C. The red clear solution gradually changed to a dark mixture. The reaction mixture was opened to air and stirred in the open flask for 12 h. The solvent was removed in vacuo and the crude product was diluted with 50% EtOAc in hexane and filtered through a layer of silica gel. The crude products were purified by flash chromatography on silica gel (15–25% gradient of EtOAc in hexane) to give the individual diastereomeric phenols **7** and/or **8** as yellowish crystals or yellowish oils. Structural and stereochemical assignment of the diastereomers as either (a*R*,7*R*; a*S*,7*S*) or as (a*R*,7*S*; a*S*,7*R*) was determined by analysis of ^{1}H NMR spectra as discussed in the text.

4.2.1. Reaction with 1-pentyne

This reaction was carried out in benzene with complex **6a** (R^1, R^2=Me) to give **7a** in 40% yield. Only one diastereomer was obtained which was identified as the (a*R*,7*R*; a*S*,7*S*) diastereomer **7** (R_L=*n*-Pr, R_S=H) and thus the diastereomeric excess (de)=100%. If the reaction was performed in CH_3CN instead of benzene, a 5.7:1 mixture of diastereomers was obtained (43% combined yield), with (a*R*,7*S*; a*S*,7*R*)-isomer **8a** predominating. Diastereomeric ratio (dr) (**8a**:**7a**)=5.7:1. Diastereomeric excess (de)=70%. The results from reactions in other solvents and under other conditions are shown in Table 1. Unless otherwise indicated in Table 1, the ratio of **7**:**8** was determined by the ratio of the weight of isolated products. In other cases indicated in Table 1, the diastereomeric ratio (dr) was determined from the ^{1}H NMR spectrum of the crude reaction mixture obtained after filtration through silica gel. Phenol **7a**: pale yellow crystals; mp 148–148.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, J=7.4 Hz, $CH_2CH_2CH_3$), 1.64–1.77 (m, 2H, $CH_3CH_2CH_2$), 2.01–2.13 (m, 1H, C6–Ha), 2.25–2.48 (m, 3H, C5–H_2, C6–Hb), 2.55–2.73 (m, 2H, $CH_3CH_2CH_2$), 3.42 (s, 3H, C7–OCH_3), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.89 (s, 6H, $2OCH_3$), 4.13 (dd, 1H, J=11.3, 5.3 Hz, C7–H), 6.55 (s, 1H, C4–H), 6.74 (s, 1H, C10–H), 8.86 (s, 1H, OH, exchange with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.9 (CH_2), 30.2 (CH_2), 32.5 (CH_2), 36.9 (CH_2), 55.9 (CH_3), 56.4 (CH_3), 58.4 (CH_3), 60.7 (CH_3), 60.8 (CH_3), 83.5 (CH), 106.9 (CH), 112.5 (CH), 120.6 (C), 120.7 (C), 120.8 (C), 129.7 (C), 135.0 (C), 140.5 (C), 146.5 (C), 149.0 (C), 151.6 (C), 152.9 (C); IR (KBr) 3365 (s, OH), 2941 (m), 1599 (m), 1463 (s), 1069 (s) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 402 M^+ (100), 370 M^+–MeOH (60), 355 (8), 339 (12), 324 (6), 295 (6), 165 (3); HRMS (EI) calcd for $C_{23}H_{30}O_6$ *m*/*z* 402.2042, found 402.2044. Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found C, 68.49; H, 7.56. Phenol **8a**: colorless crystals, mp 158.5–159.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 0.99 (t, 3H, J=7.3 Hz, $CH_2CH_2CH_3$), 1.64–1.73 (m, 2H, $CH_3CH_2CH_2$), 2.11–2.23 (m, 2H, C6–H_2), 2.29–2.35 (m, 2H, C5–H_2), 2.69 (dd, 2H, J=9.1, 6.6 Hz, $CH_3CH_2CH_2$), 2.81 (s, 3H, C7–OCH_3), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.11 (dd, 1H, J=6.0, 1.4 Hz, C7–H), 6.55 (s, 1H, C4–H), 6.77 (s, 1H, OH), 6.80 (s, 1H, C10–H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J=7.4 Hz, $CH_2CH_2CH_3$), 1.65–1.78 (m, 2H, $CH_3CH_2CH_2$), 2.18–2.40 (m, 3H, C5–Ha, C6–H_2), 2.42–2.53 (m, 1H, C5–Hb), 2.53–2.67 (m, 2H, $CH_3CH_2CH_2$), 2.92 (s, 3H, C7–OCH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H,

OCH_3), 4.42 (s, 1H, OH), 5.05–5.11 (br s, 1H, C7–H), 6.53 (s, 1H, C4–H), 6.71–6.77 (br s, 1H, C10–H); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.3 (CH_3), 24.0 (CH_2), 31.2 (CH_2), 33.5 (CH_2), 40.0 (CH_2), 55.6 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 60.5 (CH_3), 60.7 (CH_3), 74.6 (CH), 107.4 (CH), 113.2 (CH), 123.9 (C), 124.8 (C), 128.0 (C), 129.7 (C), 136.5 (C), 141.3 (C), 146.6 (C), 151.8 (C), 152.7 (C), 153.1 (C); IR (KBr) 3458 (s, OH), 3215 (s, OH), 2934 (s), 1600 (m), 1477 (s), 1225 (s) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 402 M^+ (31), 370 M^+–MeOH (100), 355 (12), 339 (20), 324 (11), 295 (5), 185 (10); HRMS (EI) calcd for $C_{23}H_{30}O_6$ *m/z* 402.2042, found 402.2056. Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found C, 68.49; H, 7.78.

4.2.2. Reaction with trimethylsilylacetylene

This reaction was carried out in benzene with complex **6e** (R^1=Me, R^2=Et) to give **7g** in 45% yield. Only one diastereomer was obtained which was identified as the (a*R*,7*R*; a*S*,7*S*) diastereomer **7** (R_L=TMS, R_S=H). Diastereomeric excess (de)=100%. Phenol **7g**: pale yellow crystals, mp 129.8–131.3 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 0.33 (s, 9H, $Si(CH_3)_3$), 1.18 (t, 3H, *J*=7.0 Hz, CHaHbCH_3), 2.02–2.10 (m, 1H, C6–Ha), 2.30–2.38 (m, 2H, C5–Ha, C6–Hb), 2.39–2.45 (m, 1H, C5–Hb), 3.41 (s, 3H, C7–OCH_3), 3.72 (s, 3H, OCH_3), 3.79–3.85 (m, 1H, C*H*aHbCH_3), 3.85–3.91 (m, 1H, CHa*H*bCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.13 (dd, 1H, *J*=11.8, 5.6 Hz, C7–H), 6.53 (s, 1H, C4–H), 6.95 (s, 1H, C10–H), 8.80 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.86 (CH_3), 15.2 (CH_3), 30.2 (CH_2), 36.8 (CH_2), 55.9 (CH_3), 58.3 (CH_3), 60.83 (CH_3), 60.85 (CH_3), 65.8 (CH_2), 83.4 (CH), 106.6 (CH), 119.8 (C), 120.2 (CH), 121.0 (C), 126.1 (C), 126.4 (C), 134.8 (C), 140.4 (C), 148.7 (C), 151.7 (C), 152.9 (C), 153.9 (C); IR (KBr) 3327 (s, OH), 2936 (s), 1595 (m), 1459 (s), 1400 (s), 1228 (m), 1119 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 446 M^+ (62), 414 M^+–MeOH (100), 399 (22), 354 (21), 338 (32); HRMS (EI) calcd for $C_{24}H_{34}O_6Si$ 446.2125, found 446.2128. Anal. Calcd for $C_{24}H_{34}O_6Si$: C, 64.54; H, 7.67. Found C, 64.50; H, 7.64.

4.2.3. Reaction with phenylacetylene

This reaction was carried out in benzene with complex **6e** (R^1=Me, R^2=Et) to give **7h** in 39% yield. Only one diastereomer was obtained which was identified as the (a*R*,7*R*; a*S*,7*S*) diastereomer **7** (R_L=Ph, R_S=H). Diastereomeric excess (de)=100%. Phenol **7h**: yellowish crystals, mp 150.3–151.0 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 2.08–2.17 (m, 1H, C6–Ha), 2.33–2.42 (m, 2H, C5–Ha, C6–Hb), 2.42–2.51 (m, 1H, C5–Hb), 3.44 (s, 3H, C7–OCH_3), 3.76 (s, 3H, OCH_3), 3.86–3.97 (m, 2H, CH_2CH$_3$), 3.906 (s, 3H, OCH_3), 3.909 (s, 3H, OCH_3), 4.22 (dd, 1H, *J*=11.7, 5.9 Hz, C7–H), 6.56 (s, 1H, C4–H), 6.95 (s, 1H, C10–H), 7.32 (t, 1H, *J*=7.4 Hz, Ph), 7.43 (t, 2H, *J*=7.7 Hz, Ph), 7.67 (d, 2H, *J*=7.6 Hz, Ph), 9.13 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (CH_3), 30.2 (CH_2), 36.9 (CH_2), 55.9 (CH_3), 58.5 (CH_3), 60.8 (CH_3), 65.5 (CH_2), 83.7 (CH), 106.8 (CH), 115.8 (CH), 120.6 (C), 121.3 (C), 124.1 (C), 126.7 (CH), 127.9 (CH), 128.7 (C), 129.4 (CH), 134.8 (C), 138.7 (C), 140.5 (C), 145.9 (C), 149.0 (C), 151.8 (C), 153.0 (C), based on integration, the signal at 60.8 ppm may contain 2 (CH_3); IR (KBr) 3310 (s, OH), 2933 (s), 1599 (m), 1458 (s), 1328 (m), 1233 (m), 1084 (s) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 450 M^+ (45), 418 M^+–MeOH (100), 389 (9), 358 (22), 303 (10), 234 (24). Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found C, 72.03; H, 6.52.

4.2.4. Reaction with tert-butylacetylene

This reaction was carried out in benzene with complex **6e** (R^1=Me, R^2=Et) to give **7i** in 43% yield. Only one diastereomer was obtained which was identified as the (a*R*,7*R*; a*S*,7*S*) diastereomer **7** (R_L=*t*-Bu, R_S=H). Diastereomeric excess (de)=100%. Phenol **7i**: yellowish crystals, mp 149.5–151 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 2.03–2.13 (m, 1H, C6–Ha), 2.25–2.36 (m, 2H, C5–Ha, C6–Hb), 2.37–2.45 (m, 1H, C5–Hb), 3.41 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.73–3.89 (m, 2H, CH_2CH$_3$), 3.891 (s, 3H, OCH_3), 3.893 (s, 3H, OCH_3), 4.16 (dd, 1H, *J*=11.7, 5.6 Hz, C7–H), 6.53 (s, 1H, C4–H), 6.91 (s, 1H, C10–H), 9.04 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (CH_3), 29.5 (CH_3), 30.3 (CH_2), 35.0 (C), 36.7 (CH_2), 55.8 (CH_3), 58.2 (CH_3), 60.77 (CH_3), 60.82 (CH_3), 65.9 (CH_2), 83.8 (CH), 106.6 (CH), 113.4 (CH), 120.4 (C), 120.9 (C), 122.3 (C), 134.8 (C), 136.5 (C), 140.3 (C), 148.15 (C), 148.19 (C), 151.7 (C), 152.6 (C); IR (CH_2Cl_2) 3303 (s, OH), 1597 (m), 1424 (s) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 430 M^+ (100), 399 M^+–MeO (63), 383 M^+–MeOH–Me (40), 369 (32), 355 (17), 338 (47), 323 (27), 264 (30), 233 (52), 84 (48), 49 (46); HRMS (EI) calcd for $C_{25}H_{34}O_6$ 430.2355, found 430.2356. Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found C, 69.74; H, 8.28.

4.2.5. Reaction with 3-hexyne

This reaction was carried out in benzene with complex **6e** (R^1=Me, R^2=Et) to give **7j** in 58% yield. Only one diastereomer was obtained which was identified as the (a*R*,7*R*; a*S*,7*S*) diastereomer **7** (R_L=Et, R_S=Et). Diastereomeric excess (de)=100%. Phenol **7j**: yellowish oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, 3H, *J*=7.1 Hz, CH_2CH_3), 1.206 (t, 3H, *J*=7.4 Hz, CH_2CH_3), 1.214 (t, 3H, *J*=7.4 Hz, CH_2CH_3), 1.98–2.09 (m, 1H, C6–Ha), 2.28–2.38 (m, 2H, C5–Ha, C6–Hb), 2.39–2.48 (m, 1H, C5–Hb), 2.63–2.78 (m, 4H, 2CH_2CH$_3$), 3.01–3.08 (m, 1H, C*H*aHbCH_3), 3.34–3.41 (m, 1H, CHa*H*bCH_3), 3.42 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.10 (dd, 1H, *J*=11.7, 5.8 Hz, C7–H), 6.53 (s, 1H, C4–H), 8.96 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (CH_3), 15.6 (CH_3), 15.8 (CH_3), 19.7 (CH_2), 20.0 (CH_2), 30.2 (CH_2), 36.7 (CH_2), 55.9 (CH_3), 58.4 (CH_3), 60.8 (CH_3), 68.6 (CH_2), 83.5 (CH), 106.4 (CH), 117.5 (C), 121.7 (C), 124.8 (C), 130.0 (C), 134.7 (C), 135.3 (C), 140.7 (C), 147.7 (C), 148.5 (C), 151.5 (C), 152.8 (C), one (CH_3) couldn't be located: based on integration, the signal at 60.8 ppm may contain 2 (CH_3);

IR (neat) 3326 (s, OH), 1597 (m), 1436 (s), 1262 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 430 M^+ (94), 398 M^+-MeOH (92), 369 (72), 338 (100), 323 (23), 309 (12); HRMS (EI) calcd for $C_{25}H_{34}O_6$ *m/z* 430.2355, found 430.2358. Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found C, 69.68; H, 8.31.

*4.3. Benzannulation reaction of carbene complexes **9** with alkynes*

The reactions were performed with the procedure described above for the reactions of complexes **6** with the exception that the reaction time was 24 h in all cases. The preparation of the carbene complexes **9** has been previously described as well as the reaction of several complexes with 1-pentyne.[9] Purification of the crude product by flash chromatography on silica gel (15% and then 25% EtOAc in hexane) led to the separation and isolation of the diastereomeric phenols **10** and **11** as yellowish crystals or yellowish oils. Structural and stereochemical assignment of the diastereomers was performed by the analysis of ^1H NMR spectra as described in the text and confirmed by X-ray crystallographic analysis of **11a**.

*4.3.1. Reaction of 1-pentyne with complex **9a** (R^1, R^2=Me)*

This reaction was carried out in benzene to give the (a*R*,7*R*; a*S*,7*S*) diastereomer **10a** in 13% yield and the (a*R*,7*S*; a*S*,7*R*) diastereomer **11a** in 40% yield. Diastereomeric excess (de)=50%. Phenol **11a** (R^1=Me, R^2=Me, R_L=Pr, R_S=H): yellowish crystals, mp 104.5–105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J*=7.4 Hz, $CH_2CH_2CH_3$), 1.63–1.75 (m, 2H, $CH_3CH_2CH_2$), 2.19–2.29 (m, 1H, C5–Ha), 2.31–2.48 (m, 3H, C5–Hb, C6–H_2), 2.65–2.79 (m, 2H, $CH_3CH_2CH_2$), 2.90 (s, 3H, C7–OCH_3), 3.72 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.88 (s, 6H, $2OCH_3$), 5.07 (d, 1H, *J*=5.5 Hz, C7–H), 6.63 (s, 1H, C4–H), 6.70 (s, 1H, OH, exchange with D_2O), 6.78 (s, 1H, C9–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 23.4 (CH_2), 31.1 (CH_2), 33.3 (CH_2), 39.9 (CH_2), 55.8 (CH_3), 56.2 (CH_3), 56.7 (CH_3), 61.1 (CH_3), 61.9 (CH_3), 73.8 (CH), 108.6 (CH), 112.9 (CH), 123.0 (C), 124.9 (C), 125.5 (C), 132.1 (C), 137.5 (C), 140.3 (C), 145.8 (C), 149.2 (C), 151.1 (C), 152.3 (C); IR (mix. of diastereomers) (CH_2Cl_2) 3378 (s, OH), 1597 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 402 M^+ (100), 371 M^+-MeO (20), 339 (34), 323 (9), 281 (7), 221 (9), 181 (6); HRMS (EI) calcd for $C_{23}H_{30}O_6$ *m/z* 402.2042, found 402.2042. Anal. (mix. of diastereomers) Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found C, 68.66; H, 7.61. Phenol **10a** (R^1=Me, R^2=Me, R_L=Pr, R_S=H): yellowish crystals, 107.5–108 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J*=7.5 Hz, $CH_2CH_2CH_3$), 1.60–1.74 (m, 2H, $CH_3CH_2CH_2$), 2.10–2.34 (m, 3H, C5–Ha, C6–H_2), 2.39–2.45 (m, 1H, C5–Hb), 2.64–2.74 (m, 2H, $CH_3CH_2CH_2$), 3.22 (s, 3H, C7–OCH_3), 3.66 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.99 (dd, 1H, *J*=11.4, 6.3 Hz, C7–H), 6.54 (s, 1H, OH, exchange with D_2O), 6.63 (s, 1H, C4–H), 6.81 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 23.4 (CH_2), 30.8 (CH_2), 33.0 (CH_2), 37.7 (CH_2), 56.0 (CH_3), 56.7 (CH_3), 57.4 (CH_3), 61.4 (CH_3), 61.8 (CH_3), 81.3 (CH), 109.0 (CH), 114.5 (CH), 121.4 (C), 123.7 (C), 124.1 (C), 131.1 (C), 137.1 (C), 140.5 (C), 144.8 (C), 149.1 (C), 150.6 (C), 153.0 (C); IR (mix. of diastereomers) (CH_2Cl_2) 3378 (s, OH), 1597 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 402 M^+ (100), 371 M^+-MeO (16), 339 (21), 323 (5), 295 (4), 221 (6), 181 (5); HRMS (EI) calcd for $C_{23}H_{30}O_6$ *m/z* 402.2042, found 402.2036. Anal. (mix. of diastereomers) Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found C, 68.66; H, 7.61.

*4.3.2. Reaction of 1-pentyne with complex **9g** (R^1=t-Bu, R^2=i-Pr)*

This reaction was carried out in benzene to give the (a*R*,7*R*; a*S*,7*S*) diastereomer **10g** in 11% yield and the (a*R*,7*S*; a*S*,7*R*) diastereomer **11g** in 37% yield. Diastereomeric excess (de)=55%. Phenol **11g** (R^1=*t*-Bu, R^2=*i*-Pr, R_L=Pr, R_S=H): yellowish oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H, $C(CH_3)_3$), 0.97 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$), 1.34 (d, 3H, *J*=6.1 Hz, CH_3CHCH_3), 1.35 (d, 3H, *J*=6.1 Hz, CH_3CHCH_3), 1.63–1.71 (m, 2H, $CH_3CH_2CH_2$), 2.04–2.15 (m, 1H, C5–Ha), 2.25–2.47 (m, 3H, C5–Hb, C6–H_2), 2.66–2.71 (m, 2H, $CH_3CH_2CH_2$), 3.71 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.46 (septet, 1H, *J*=6.1 Hz, CH_3CHCH_3), 5.27 (d, 1H, *J*=5.3 Hz, C7–H), 6.62 (s, 1H, C4–H), 6.67 (s, 1H, OH), 6.71 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.3 (CH_3), 22.4 (CH_3), 23.3 (CH_2), 27.9 (CH_3), 31.1 (CH_2), 33.1 (CH_2), 42.5 (CH_2), 56.0 (CH_3), 61.2 (CH_3), 61.3 (CH_3), 63.9 (CH), 70.8 (CH), 73.1 (C), 108.8 (CH), 115.4 (CH), 124.2 (C), 125.3 (C), 130.7 (C), 130.9 (C), 138.1 (C), 140.1 (C), 145.5 (C), 146.4 (C), 148.9 (C), 151.9 (C); IR (mix. of diastereomers) (CH_2Cl_2) 3368 (s, OH), 1421 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 472 M^+ (85), 356 M^+-t-BuOH–CH_3CHCH_2 (77), 313 (21), 181 (100), 57 (100); HRMS (EI) calcd for $C_{28}H_{40}O_6$ *m/z* 472.2825, found 472.2828. Phenol **10g** (R^1=*t*-Bu, R^2=*i*-Pr, R_L=Pr, R_S=H): yellowish oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J*=7.3 Hz, $CH_2CH_2CH_3$), 1.01 (s, 9H, $C(CH_3)_3$), 1.31 (d, 3H, *J*=6.1 Hz, CH_3CHCH_3), 1.37 (d, 3H, *J*=6.1 Hz, CH_3CHCH_3), 1.59–1.70 (m, 2H, $CH_3CH_2CH_2$), 2.00–2.26 (m, 3H, C5–Ha, C6–H_2), 2.35–2.42 (m, 1H, C5–Hb), 2.60–2.72 (m, 2H, $CH_3CH_2CH_2$), 3.70 (s, 3H, OCH_3), 3.91 (s, 6H, $2OCH_3$), 4.19 (dd, 1H, *J*=11.2, 6.8 Hz, C7–H), 4.50 (septet, 1H, *J*=6.1 Hz, CH_3CHCH_3), 6.50 (s, 1H, OH), 6.65 (s, 1H, C4–H), 6.77 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.1 (CH_3), 22.7 (CH_3), 23.3 (CH_2), 27.8 (CH_3), 31.3 (CH_2), 32.8 (CH_2), 40.3 (CH_2), 56.1 (CH_3), 61.4 (CH_3), 62.0 (CH_3), 71.2 (CH), 71.4 (CH), 73.8 (C), 108.9 (CH), 120.4 (CH), 121.8 (C), 122.8 (C), 130.0 (C), 130.2 (C), 137.4 (C), 140.6 (C), 144.9 (C), 149.2 (C), 152.9 (C), one (C) could not be located; IR (mix. of diastereomers) (CH_2Cl_2) 3368 (s, OH), 1421 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 472 M^+ (29), 356 M^+-t-BuOH–CH_3CHCH_2 (34), 232 (24), 149 (100), 57 (54); HRMS (EI) calcd for $C_{28}H_{40}O_6$ *m/z* 472.2825, found 472.2827.

*4.3.3. Reaction of 1-pentyne with complex **9h** (R^1=Me, R^2=MOM)*

This reaction was carried out in benzene to give the (a*R*,7*R*; a*S*,7*S*) diastereomer **10h** in 9% yield and the (a*R*,7*S*; a*S*,7*R*) diastereomer **11h** in 30% yield. Diastereomeric ratio (dr)=3.0:1. Diastereomeric excess (de)=50%. Phenol **11h** (R^1=Me, R^2=MOM, R_L=Pr, R_S=H): yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, 3H, J=7.4 Hz, CH_3CH$_2$CH$_2$), 1.61–1.75 (m, 2H, CH$_3$CH_2CH$_2$), 2.26 (td, 1H, J=13.6, 5.5 Hz, C5–Ha), 2.32–2.40 (m, 2H, C6–H$_2$), 2.45 (td, 1H, J=13.3, 6.5 Hz, C5–Hb), 2.65–2.75 (m, 2H, CH$_3$CH$_2$CH_2), 2.92 (s, 3H, C7–OMe), 3.52 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.89 (s, 3H, OMe), 5.07 (d, 1H, J=6.2 Hz, C7–H), 5.13 (d, 1H, J=6.5 Hz, CH$_3$OC*H*aHb), 5.17 (d, 1H, J=6.5 Hz, CH$_3$OCHa*H*b), 6.63 (s, 1H, C4–H), 6.73 (s, 1H, OH), 6.94 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 23.2 (CH_2), 30.9 (CH_2), 33.1 (CH_2), 39.9 (CH_2), 55.7 (CH_3), 56.1 (CH_3), 56.1 (CH_3), 61.1 (CH_3), 61.9 (CH_3), 74.1 (CH), 96.0 (CH_2), 108.5 (CH), 116.5 (CH), 122.7 (C), 124.5 (C), 126.4 (C), 132.4 (C), 137.4 (C), 140.2 (C), 146.8 (C), 148.7 (C), 149.1 (C), 152.3 (C); IR (mix. of diastereomers) (CH_2Cl_2) 3354 (s, OH), 1608 (m), 1423 (m), 1261 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 432 M^+ (97), 401 M^+–MeO (7), 400 M^+–MeOH (8), 356 M^+–MeO–MeOCH$_2$ (100), 324 (26), 313 (16), 181 (17); HRMS (EI) calcd for $C_{24}H_{32}O_7$ *m*/*z* 432.2148, found 432.2140. Anal. (mix. of diastereomers) Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found C, 66.77; H, 7.61. Phenol **10h** (R^1=Me, R^2=MOM, R_L=Pr, R_S=H): yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, 3H, J=7.4 Hz, CH_3CH$_2$CH$_2$), 1.62–1.73 (m, 2H, CH$_3$CH_2CH$_2$), 2.10–2.16 (m, 1H, C6–Ha), 2.23–2.34 (m, 2H, C6–Hb, C5–Ha), 2.41–2.46 (m, 1H, C5–Hb), 2.68 (t, 2H, J=7.7 Hz, CH$_3$CH$_2$CH_2), 3.26 (s, 3H, C7–OMe), 3.58 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.01 (dd, 1H, J=11.4, 6.0 Hz, C7–H), 5.16 (s, 2H, CH$_3$OCH_2), 6.54 (s, 1H, OH), 6.65 (s, 1H, C4–H), 7.02 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 23.3 (CH_2), 30.7 (CH_2), 32.8 (CH_2), 38.0 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 57.4 (CH_3), 61.3 (CH_3), 61.8 (CH_3), 81.2 (CH), 96.6 (CH_2), 108.9 (CH), 119.5 (CH), 121.1 (C), 123.7 (C), 125.1 (C), 131.4 (C), 136.9 (C), 140.5 (C), 146.1 (C), 148.1 (C), 149.2 (C), 153.0 (C); IR (mix. of diastereomers) (CH_2Cl_2) 3354 (s, OH), 1608 (m), 1423 (m), 1261 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 432 M^+ (83), 402 (16), 401 M^+–MeO (5), 400 M^+–MeOH (7), 387 M^+–MeOCH$_2$ (6), 356 M^+–MeO–MeOCH$_2$ (100), 324 (27), 313 (14), 181 (21); HRMS (EI) calcd for $C_{24}H_{32}O_7$ *m*/*z* 432.2148, found 432.2151. Anal. (mix. of diastereomers) Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found C, 66.77; H, 7.61.

*4.3.4. Reaction of trimethylsilylacetylene with complex **9c** (R^1=i-Pr, R^2=Me)*

This reaction was carried out in benzene to give the (a*R*,7*R*; a*S*,7*S*) diastereomer **10i** in 22% yield and the (a*R*,7*S*; a*S*,7*R*) diastereomer **11i** in 29% yield. Diastereomeric ratio (dr)=1.3:1. Diastereomeric excess (de)=13%. Phenol **11i** (R^1=*i*-Pr, R^2=Me, R_L=TMS, R_S=H): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.34 (s, 9H, Si(CH$_3$)$_3$), 0.73 (d, 3H, J=6.2 Hz, CH_3CHCH$_3$), 0.91 (d, 3H, J=6.1 Hz, CH$_3$CHCH_3), 2.21–2.30 (m, 2H, C6–H$_2$), 2.36–2.42 (m, 1H, C5–Ha), 2.48 (td, 1H, J=12.7, 7.9 Hz, C5–Hb), 3.21 (septet, 1H, J=6.1 Hz, CH$_3$C*H*CH$_3$), 3.77 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.89 (s, 3H, OMe), 5.37 (d, 1H, J=4.9 Hz, C7–H), 6.65 (s, 1H, C4–H), 6.86 (s, 1H, OH), 6.97 (s, 1H, C9–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.8 (CH_3), 20.7 (CH_3), 22.9 (CH_3), 30.9 (CH_2), 39.2 (CH_2), 55.9 (CH_3), 56.6 (CH_3), 61.1 (CH_3), 61.4 (CH_3), 66.6 (CH), 67.6 (CH), 108.7 (CH), 116.9 (CH), 122.8 (C), 124.8 (C), 128.3 (C), 130.2 (C), 137.9 (C), 140.1 (C), 148.7 (C), 150.6 (C), 152.3 (C), 152.5 (C); IR (mix. of diastereomers) (KBr) 3397 (s, OH), 1601 (m), 1464 (s), 1376 (m), 1125 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 460 M^+ (100), 385 (7), 370 (5), 369 (8), 181 (7), 149 (8). Anal. (mix. of diastereomers) Calcd for $C_{25}H_{36}O_6Si$: C, 65.19; H, 7.88. Found C, 65.54; H, 7.55. Phenol **10i** (R^1=*i*-Pr, R^2=Me, R_L=TMS, R_S=H): yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.34 (s, 9H, Si(CH$_3$)$_3$), 0.92 (d, 3H, J=6.1 Hz, CH_3CHCH$_3$), 1.15 (d, 3H, J=6.1 Hz, CH$_3$CHCH_3), 2.17–2.29 (m, 3H, C5–Ha, C6–H$_2$), 2.42–2.47 (m, 1H, C5–Hb), 3.52 (septet, 1H, J=6.1 Hz, CH$_3$C*H*CH$_3$), 3.67 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.28 (dd, 1H, J=9.8, 7.8 Hz, C7–H), 6.65 (s, 1H, C4–H), 6.72 (s, 1H, OH), 7.00 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.9 (CH_3), 20.4 (CH_3), 23.1 (CH_3), 31.0 (CH_2), 38.2 (CH_2), 56.0 (CH_3), 56.6 (CH_3), 61.4 (CH_3), 61.8 (CH_3), 69.2 (CH), 75.5 (CH), 109.2 (CH), 119.0 (CH), 121.2 (C), 123.6 (C), 127.5 (C), 129.4 (C), 137.2 (C), 140.6 (C), 149.1 (C), 151.4 (C), 151.6 (C), 153.0 (C); IR (mix. of diastereomers) (KBr) 3397 (s, OH), 1601 (m), 1464 (s), 1376 (m), 1125 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 460 M^+ (100), 417 (5), 385 (9), 370 (7), 369 (11), 181 (10), 149 (5). Anal. (mix. of diastereomers) Calcd for $C_{25}H_{36}O_6Si$: C, 65.19; H, 7.88. Found C, 65.54; H, 7.55.

*4.4. Benzannulation reaction of carbene complex **9a** with tert-butylacetylene*

To a solution of **9a** (0.323 g, 0.649 mmol) in dry benzene (1.95 mL) in a single necked pear shaped flask in which the 14/20 joint was replaced with a threaded high-vacuum Teflon stopcock was added a 3-fold excess of 3,3-dimethyl-but-1-yne (0.160 g, 1.946 mmol) and the resulting solution was deoxygenated by the freeze–pump–thaw method (−196 °C/25 °C, three cycles). The flask was back-filled with argon (conditions 1) or CO (conditions 2) at room temperature, closed, and then heated for 24 h at 55–58 °C. The clear red solution gradually changed to dark opaque solution. The reaction mixture was opened to air and stirred in the open flask for 12 h. The solvent was removed in vacuo and the crude product was diluted with 50% EtOAc in hexane and filtered through a layer of silica gel. The solvent was removed in vacuo, the residue was dissolved in ether (2 mL), then I_2 (0.033 g, 0.130 mmol) was added, and

the mixture was stirred at room temperature for 15 min. The reaction was quenched with excess of saturated aqueous $Na_2S_2O_3$ solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$, the solvent was removed, and the residue was filtered through a layer of silica gel (50% EtOAc in hexane) giving, after solvent removal, a crude mixture of products. The product ratio was then measured from the crude mixture by ^{1}H NMR. Purification by flash chromatography on silica gel (20% EtOAc in hexane, followed by 25% and 50% mixtures) gave the individual diastereomeric phenols **10k** and **11k** and the cyclopentenone derivatives **12** and **13**.

Conditions 1. Under Ar: phenol **11k** (a*R*,7*S*; a*S*,7*R*):phenol **10k** (a*R*,7*R*; a*S*,7*S*):cyclopentenone **13**:cyclopentenone **12**=7.0:1.0:4.9:2.4. Combined yield of **10k** and **11k**: 0.085 g (32%). Combined yield of **12** and **13**: 0.070 g (29%).

Conditions 2. Under CO: phenol **11k** (a*R*,7*S*; a*S*,7*R*):phenol **10k** (a*R*,7*R*; a*S*,7*S*):cyclopentenone **13**:cyclopentenone **12**=7.0:1.0:4.0:1.7. Combined yield of **11k** and **10k**: 0.085 g (39%). Combined yield of **12** and **13**: 0.070 g (21%).

4.4.1. Phenol ***11k*** *(major)*

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, $C(CH_3)_3$), 2.17–2.51 (m, 4H, C5–H_2, C6–H_2), 2.91 (s, 3H, C7–OMe), 3.70 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.05 (d, 1H, J=6.0 Hz, C7–H), 6.63 (s, 1H, C4–H), 6.73 (s, 1H, OH), 6.95 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (CH_3), 31.1 (CH_2), 35.4 (C), 39.7 (CH_2), 55.8 (CH_3), 56.3 (CH_3), 57.0 (CH_3), 61.2 (CH_3), 61.8 (CH_3), 73.7 (CH), 108.7 (CH), 110.6 (CH), 123.0 (C), 125.7 (C), 125.9 (C), 137.6 (C), 139.3 (C), 140.4 (C), 146.8 (C), 149.3 (C), 150.9 (C), 152.4 (C); IR (mix. of diastereomers) (KBr) 3396 (s, OH), 1599 (m), 1456 (s), 1123 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 416 M^+ (100), 369 (14), 353 (18), 286 (9), 249 (7), 233 (11), 149 (25); HRMS (EI) calcd for $C_{24}H_{32}O_6$ *m*/*z* 416.2199, found 416.2195. Anal. (mix. of diastereomers) Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found C, 68.94; H, 7.95.

4.4.2. Phenol ***10k*** *(minor)*

Yellowish oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 2.10–2.17 (m, 1H, C6–Ha), 2.23–2.31 (m, 2H, C6–Hb, C5–Ha), 2.40–2.46 (m, 1H, C5–Hb), 3.25 (s, 3H, C7–OMe), 3.65 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.97 (dd, 1H, J=11.7, 5.3 Hz, C7–H), 6.58 (s, 1H, OH), 6.65 (s, 1H, C4–H), 6.99 (s, 1H, C9–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8 (CH_3), 30.8 (CH_2), 35.2 (C), 37.7 (CH_2), 56.1 (CH_3), 57.1 (CH_3), 57.5 (CH_3), 61.4 (CH_3), 61.7 (CH_3), 81.2 (CH), 109.1 (CH), 112.6 (CH), 121.4 (C), 124.2 (C), 125.1 (C), 137.1 (C), 138.3 (C), 140.6 (C), 145.8 (C), 149.2 (C), 150.3 (C), 153.0 (C); IR (mix. of diastereomers) (KBr) 3396 (s, OH), 1599 (m), 1456 (s), 1123 (m) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 416 M^+ (100), 369 (12), 353 (15), 294 (5), 248 (9); HRMS (EI) calcd for $C_{24}H_{32}O_6$ *m*/*z* 416.2199, found 416.2193. Anal. (mix. of diastereomers) Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found C, 68.94; H, 7.95.

4.4.3. Cyclopentenone ***13*** *(major)*

Colorless crystals, mp 102.3–103.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 9H, $C(CH_3)_3$), 2.25 (td, 1H, J=14.3, 5.3 Hz, C6–Ha), 2.42–2.51 (m, 3H, C5–Ha, C6–Hb, C9–Ha), 2.57–2.69 (m, 2H, C5–Hb, C9–Hb), 2.94 (s, 3H, C7–OMe), 3.76 (dd, 1H, J=6.9, 1.6 Hz, C10–H), 3.80 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.40 (d, 1H, J=7.0 Hz, C7–H), 6.57 (s, 1H, C4–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9 (CH_3), 31.9 (CH_2), 35.0 (C), 38.9 (CH_2), 40.0 (CH_2), 50.0 (CH), 55.7 (CH_3), 55.9 (CH_3), 60.9 (CH_3), 61.1 (CH_3), 70.4 (CH), 108.2 (CH), 124.0 (C), 135.9 (C), 140.6 (C), 142.2 (C), 151.6 (C), 153.8 (C), 175.3 (C), 207.6 (C); IR (mix. of diastereomers) (KBr) 2939 (s), 1698 (s, CO), 1595 (m), 1467 (m), 1283 (m), 1109 (s) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 374 M^+ (100), 359 M^+–Me (10), 344 M^+–2Me (22), 303 (14), 286 (72), 271 (19), 258 (10), 243 (14), 231 (8), 229 (9). Anal. (mix. of diastereomers) Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found C, 70.48; H, 8.22.

4.4.4. Cyclopentenone ***12*** *(minor)*

Yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (s, 9H, $C(CH_3)_3$), 2.14–2.22 (m, 1H, C6–Ha), 2.36–2.45 (m, 1H, C6–Hb), 2.45 (dd, 1H, J=18.5, 1.4 Hz, C9–Ha), 2.48–2.59 (m, 2H, C5–H_2), 2.64 (dd, 1H, J=18.5, 6.9 Hz, C9–Hb), 3.31 (s, 3H, C7–OMe), 3.62 (d, 1H, J=6.9 Hz, C10–H), 3.79 (ddd, 1H, J=10.9, 3.8, 1.5 Hz, C7–H), 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.59 (s, 1H, C4–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9 (CH_3), 30.5 (CH_2), 34.9 (C), 38.7 (CH_2), 40.7 (CH_2), 49.5 (CH), 55.9 (CH_3), 58.2 (CH_3), 60.9 (CH_3), 61.0 (CH_3), 77.8 (CH), 108.2 (CH), 123.1 (C), 135.9 (C), 140.9 (C), 141.0 (C), 151.3 (C), 153.9 (C), 170.9 (C), 205.7 (C); IR (mix. of diastereomers) (KBr) 2939 (s), 1698 (s, CO), 1595 (m), 1467, 1283 (m), 1109 (s) cm^{-1}. Mass spectrum (EI) *m*/*z* (% rel intensity) 374 M^+ (35), 344 M^+–2Me (100), 287 (80), 271 (17), 259 (12), 243 (14), 231 (9), 229 (9). Anal. (mix. of diastereomers) Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found C, 70.48; H, 8.22.

4.5. 8-Bromo- and 9-bromo-1,2,3-trimethoxy-6,7-dihydro-5H-benzocyclohepten-7-ones ***15*** and ***19***

The reactions were conducted employing the general TPAP/NMO oxidation procedure.[30] To a stirred solution of either the alcohol **14**[14] or **18**[9] (1 equiv) and NMO–H_2O (1.5 equiv) in dry CH_2Cl_2 (~0.5 M) was added TPAP (0.05 equiv) under argon, followed by powdered molecular sieves MS 4 Å (0.25 g/mL). The reaction was monitored by TLC. After stirring at room temperature for 1 h the ratio of

ketone and alcohol had stabilized and didn't change with additional time. After 2 h of stirring, the mixture was filtered through a layer of silica gel (35% EtOAc in hexane), the solvent was removed, and the residue was purified by column chromatography on silica gel.

4.5.1. Ketone **19**

The crude product was purified by silica gel chromatography with 20% EtOAc in hexane to give the target ketone **19** as a yellow oil (75%) along with a 15% recovery of the starting alcohol **18**. The ketone solidified upon storage. Ketone **19**: yellowish crystals, 76.6–77.8 °C (ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45–2.77 (br s, 2H, C5–H_2), 2.77–3.25 (br s, 2H, C6–H_2), 3.84 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.00 (s, 3H, OMe), 6.52 (s, 1H, C4–H), 6.79 (s, 1H, C8–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1 (CH_2)), 46.0 (CH_2), 55.9 (CH_3), 60.7 (CH_3), 61.2 (CH_3), 106.2 (CH), 121.9 (C), 132.9 (C), 134.4 (CH), 136.0 (C), 141.3 (CH), 153.3 (C), 154.9 (C), 200.6 (C); IR (KBr) 2943 (m), 1679 (s, CO), 1591 (s), 1348 (m), 1119 (s) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 328 M^+ (97, ^{81}Br), 326 M^+ (100, ^{79}Br), 300 (28, ^{81}Br), 298 (28, ^{79}Br), 285 (9, ^{81}Br), 283 (9, ^{79}Br), 247 M^+–Br (58), 232 (12), 219 (96), 205 (51), 188 (39), 161 (19), 115 (21), 102 (15); HRMS (EI) calcd for $C_{14}H_{15}^{79}BrO_4$ *m/z* 326.0154, found 326.0159.

4.5.2. Ketone **15**

The crude product was purified by silica gel chromatography with 2% ether in CH_2Cl_2 to give the target ketone **15** as a yellow solid (76%) along with 18% recovery of the starting alcohol **14**. Ketone **15**: yellow crystals, 129.9–130.3 °C (*i*-BuCOMe/hexane) (reported[31] 128–130 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84–2.96 (m, 4H, C5–H_2, C6–H_2), 3.86 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.57 (s, 1H, C4–H), 8.29 (s, 1H, C9–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3 (CH_2)), 41.1 (CH_2), 56.0 (CH_3), 60.9 (CH_3), 61.8 (CH_3), 107.7 (CH), 120.4 (C), 123.8 (C), 138.4 (C), 138.8 (CH), 140.5 (C), 153.6 (C), 155.3 (C), 192.6 (C); IR (KBr) 2938 (m), 1666 (s, CO), 1599 (s), 1341 (s), 1125 (m) cm^{-1}. Mass spectrum (EI) *m/z* (% rel intensity) 328 M^+ (51, ^{81}Br), 326 M^+ (51, ^{79}Br), 247 M^+–Br (100), 219 (23), 204 (17), 188 (46), 161 (20), 118 (16), 57 (15); HRMS (EI) calcd for $C_{14}H_{15}^{79}BrO_4$ *m/z* 326.0154, found 326.0162. Anal. Calcd for $C_{14}H_{15}BrO_4$: C, 51.40; H, 4.62. Found C, 51.16; H, 4.77.

4.6. CBS reduction[16] of ketone 15—preparation of (R)-8-bromo-1,2,3-trimethoxy-6,7-dihydro-5H-benzocyclohepten-7-ol (R)-**14**

Glassware for the reaction was dried at 150 °C for at least 12 h and then cooled under argon. Ketone **15** was dried in vacuo (0.1 mmHg) with a heat gun for 0.5 h prior to the reaction. A solution of $BH_3\cdot SMe_2$ was prepared by dissolving the ~10 M neat complex (0.044 mL, 0.44 mmol) in 1.22 mL of dry CH_2Cl_2. To a 10 mL reaction flask filled with argon was added a 1 M toluene solution of oxazaborolidine (*S*)-**16a** (R=Me) (0.024 mL, 0.024 mmol), followed by 0.92 mL of the $BH_3\cdot SMe_2$ solution (0.33 mmol). This mixture was stirred at room temperature for 15 min, then cooled to 0 °C. Ketone **15** (0.196 g, 0.599 mmol) was added quickly as a solid and the stirring continued for 2 h at 0 °C. The solution was then warmed to room temperature and stirred for 1.5 h. The rest of $BH_3\cdot SMe_2$ solution was then added and the progress of the reaction was monitored by TLC (5% Et_2O in CH_2Cl_2) for the disappearance of the starting ketone (~1 h). The reaction was quenched with MeOH (1.2 mL), the volatiles were removed in vacuo, and the residue filtered through a short plug of silica gel (1:1 Et_2O/CH_2Cl_2) to give, after solvent removal, 0.196 g of the alcohol (*R*)-**14** (99% yield). The spectral data for this product matched those previously reported for this compound.[14] The enantiomeric purity of (*R*)-**14** was determined to be 99% ee by HPLC (Chiralcel OD column, flow rate: 1 mL/min; hexane/*i*-PrOH 98:2 to 90:10 over 15 min; t_R of (*R*)-**14**: 11.3 min; t_R of (*S*)-**14**: 12.4 min). Recrystallization from methyl ethyl ketone (by diffusion of hexane) gave enantiopure material (first crop, 89% yield); $[\alpha]_D^{20}$ +206 (*c* 1, CH_2Cl_2). The CBS reduction of ketone **15** and ketone **19** was also examined under a variety of conditions and the results are indicated in Table 4. This method was not suitable for the reduction of ketone **19**.

Table 4
Asymmetric CBS reductions of ketones **15** and **19**[a]

Ketone	(*S*)-**16**	R	(*S*)-**16** (equiv)	Alcohol	% Yield	% ee
19	**16a**	Me	1.0	(*R*)-**18**	91	10
19	**16b**	CH_2TMS	0.04	(*R*)-**18**	95	6
19	**16a**	Me	0.04	(*R*)-**18**	94	6
15	**16a**	Me	1.0	(*R*)-**14**	97	98
15	**16b**	CH_2TMS	0.04	(*R*)-**14**	97	95
15	**16a**	Me	0.04	(*R*)-**14**	99	96
15[b]	**16a**	Me	0.04	(*R*)-**14**	99	99

[a] Ketone was added as a solid to a solution of (*S*)-**16** and $BH_3\cdot SMe_2$ (0.7 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred at 0 °C for 0.5–3 h and then warmed to 25 °C.

[b] The ketone was added as a solid to a solution of (*S*)-**16** and $BH_3\cdot SMe_2$ (0.5 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred at 0 °C for 2 h and then at 25 °C for 1.5 h before additional $BH_3\cdot SMe_2$ (0.2 equiv) was added.

4.7. Asymmetric reduction[19] of ketone **19** using TarB–NO_2–$LiBH_4$

The starting ketone **19** (0.467 g, 1.428 mmol) was dried in vacuo (0.1 mmHg) with a heat gun for 0.5 h and then dissolved under argon in a 0.4 M solution of TarB–NO_2 **20** (2.856 mmol, 7.1 mL) in THF. The solution was stirred at room temperature for 0.5 h and then a 2 M $LiBH_4$ solution (1.499 mmol, 0.75 mL) in THF was added over 20 min via a syringe pump. The mixture was stirred for 10 min and then it was quenched by the dropwise addition of water (2 mL). A 10% aqueous HCl solution (2 mL) was added and the THF was removed in vacuo. The product was extracted into ether (10 mL), the organic layer separated, and then extracted with 10% aqueous NaOH solution (2×15 mL). The organic layer was separated and dried over $MgSO_4$. Solvent

removal gave 0.458 g of (*S*)-**18** (97%). The spectral data for alcohol **18** matched those previously reported for this compound.[9] The enantiomeric purity of **18** was determined to be 42% ee by HPLC (Chiralpak AS column, flow rate: 1 mL/min; hexane/*i*-PrOH 90:10 to 80:20 over 10 min, 80:20 for 1 min, and then to 90:10 over 1 min; t_R of (*R*)-**18**: 10.2 min; t_R of (*S*)-**18**: 11.1 min).

4.8. Kinetic resolution[20] of scalemic (*S*)-*18* through acetylation

Fu's catalyst **21** (0.018 g, 0.028 mmol, 2 mol %) was purchased from Strem Chemicals. It was dried in vacuo (0.1 mmHg) with a heat gun for 15 min prior to use. Alcohol (*S*)-**18** (0.458 g, 1.392 mmol, 42% ee) was dissolved in 5.4 mL of *t*-AmOH (distilled over CaH_2). To this solution was added NEt_3 (0.084 g, 0.835 mmol), followed by the catalyst and then the flask was flushed with Ar. The mixture was sonicated to dissolve the catalyst, cooled to 0 °C, and then Ac_2O (0.071 g, 0.696 mmol) was added dropwise. The solution was stirred at 0 °C under argon for 15 h, then it was filtered through the short plug of silica gel (40% EtOAc in hexane), from which the catalyst can be recovered (17 mg, 94%) by washing with a 1:1 mixture of EtOAc and Et_3N. The filtrate was analyzed by HPLC (see conditions above), which revealed that (*S*)-**18** was 99% ee at 49% conversion. The solvent was removed and the residue subjected to column chromatography (silica gel, 25% EtOAc in hexane) to give after the solvent removal, **22** (0.238 g, 46%) and (*S*)-**18** (0.234 g, 51%, 99% ee). This level of optical purity enhancement corresponds to an *s* value of the catalyst of 13.2. With a second run with the recycled catalyst the *s* value was 8.3. For runs 3–8 with the recycled catalyst the *s* value was ~5.5. The spectral data for alcohol **18** matched those previously reported for this compound.[9] Optical rotation of (*S*)-**18**: $[\alpha]_D^{20}$ −109 (*c* 1, CH_2Cl_2) on 99% ee material . Spectral data for **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98–2.03 (br s, 3H, COMe), 2.00–2.07 (m, 1H, C6–Ha), 2.44–2.56 (m, 2H, C6–Hb, C5–Ha), 2.70–2.81 (m, 1H, C5–Hb), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.97–5.03 (m, 1H, C7–H), 6.45–6.50 (br s, 1H, C8–H), 6.50 (s, 1H, C4–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (CH_3), 30.3 (CH_2), 38.5 (CH_2), 55.9 (CH_3), 60.8 (CH_3), 61.0 (CH_3), 71.6 (CH), 107.1 (CH), 113.6 (C), 122.9 (C), 134.2 (CH), 135.6 (C), 141.0 (C), 151.9 (C), 154.1 (C), 169.9 (C); IR (KBr) 2943 (m), 1736 (s), 1593 (m), 1459 (m), 1238 (s), 1119 (s) cm^{-1}. Mass spectrum (FAB$^+$) *m/z* (% rel intensity) 372 M$^+$ (74, ^{81}Br), 370 M$^+$ (74, ^{79}Br), 313 M$^+$–OCOMe (92, ^{81}Br), 311 M$^+$–OCOMe (100, ^{79}Br), 231 (43); HRMS (FAB$^+$) calcd for $C_{16}H_{19}O_5Br$ *m/z* 370.0416, found 370.0403. Anal. Calcd for $C_{16}H_{19}BrO_5$: C, 51.77; H, 5.16. Found C, 51.73; H, 5.23.

4.9. (*S*)-9-Bromo-1,2,3,7-tetramethoxy-6,7-dihydro-5H-benzocycloheptene and (*R*)-8-bromo-1,2,3,7-tetramethoxy-6,7-dihydro-5H-benzocycloheptene (*S*)-*23* and (*R*)-*17*

To a solution of (*S*)-**18** or (*R*)-**14** (1 equiv) in dry THF (7.14 mL/mmol of alcohol) was added NaH (60% in oil) (3 equiv) and the mixture was refluxed under argon for 3 h. MeI (3 equiv) was added and the reflux was continued for 15 h. TLC analysis showed full conversion in both cases. The solvent was removed in vacuo and water (7.14 mL/mmol of alcohol) was added to the residue containing the product, which was extracted twice with ether. The combined organic layers were dried over $MgSO_4$, the solvent was removed, and the crude product was purified by column chromatography (silica gel, 15% EtOAc in hexane) to give (*S*)-**23** (85%, 99% ee, $[\alpha]_D^{20}$ −159 (*c* 1, CH_2Cl_2)) or (*R*)-**17** (87%, >99% ee, $[\alpha]_D^{20}$ +183 (*c* 1, CH_2Cl_2)). Enantiomeric purity of (*S*)-**23** and (*R*)-**17** was determined by HPLC (Chiralcel OD-H column, flow rate: 0.8 mL/min; hexane/*i*-PrOH 100:0 to 98:2 over 10 min, 98:2 for 5 min; t_R of (*R*)-**23**: 14.6 min; t_R of (*S*)-**23**: 15.6 min; t_R of (*R*)-**17**: 13.0 min; t_R of (*S*)-**17**: 13.3 min).

4.10. Preparation of carbene complex (*S*)-*6a*

To a stirred solution of (*S*)-**23** (0.55 g, 1.603 mmol, 99% ee) in 22 mL of absolute THF at −78 °C was added a 1.35 M *t*-BuLi solution in pentane (3.206 mmol, 2.4 mL) dropwise under argon. The mixture was stirred at −78 °C for 15 min and then slowly (~5 min) transferred via cannula into a stirred suspension of $Cr(CO)_6$ (0.353 g, 1.603 mmol) in 33 mL of absolute THF at 0 °C. The mixture was stirred 0.5 h at 0 °C and 1.5 h at room temperature. Then the solvent was removed in vacuo, the residue dissolved in 25 mL of CH_2Cl_2, and then $Me_3O^+BF_4^-$ (0.712 g, 4.809 mmol) was added. The reaction was started by the addition of 25 mL of water. The resulting mixture was stirred for 20 min at room temperature. The red reaction mixture was quenched with 25 mL of the saturated aqueous $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted once with ether. The organic layers were combined and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was subjected to flash chromatography (silica gel, 20% EtOAc in hexane) giving, after removal of solvent, carbene complex (*S*)-**6a** (0.687 g, 86%). The spectral data for **6a** matched those previously reported for the racemic compound.[9] Enantiomeric purity of (*S*)-**6a** was determined to be 99% ee by HPLC (Chiralcel OD column, flow rate: 1 mL/min; hexane/*i*-PrOH 98:2 to 95:5 over 8 min, 95:5 to 90:10 over 7 min; t_R of (*R*)-**6a**: 6.9 min; t_R of (*S*)-**6a**: 7.9 min).

4.11. Preparation of carbene complex (*R*)-*9a*

To a stirred solution of (*R*)-**17** (0.273 g, 0.796 mmol, >99% ee) in 10 mL of absolute THF at −78 °C was added a 1.5 M *t*-BuLi solution in pentane (1.592 mmol, 1.06 mL) dropwise under argon. The mixture was stirred at −78 °C for 15 min and then slowly (~5 min) transferred via cannula into a stirred suspension of $Cr(CO)_6$ (0.175 g, 0.796 mmol) in 15 mL of absolute THF at 0 °C. The mixture was stirred 0.5 h at 0 °C and 1.5 h at room temperature. Then the solvent was removed in vacuo, the residue dissolved in 15 mL of CH_2Cl_2, and then $Me_3O^+BF_4^-$ (0.353 g, 2.388 mmol) was added. The reaction

was started by the addition of 15 mL of water. The resulting mixture was stirred for 20 min at room temperature. The red reaction mixture was quenched with 15 mL of the saturated aqueous $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted once with ether. The organic layers were combined and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was subjected to flash chromatography (silica gel, 20% EtOAc in hexane) giving, after removal of solvent, carbene complex (*R*)-**9a** together with 5–10% of the tetracarbonyl chelate complex (0.309 g, 78%). The spectral data of **9a** matched those previously reported for the racemic compound.[9] The enantiomeric purity of (*R*)-**9a** was determined to be >99% ee by HPLC (Chiralcel OD column, flow rate: 1 mL/min; hexane/*i*-PrOH 98:2 to 95:5 over 8 min, 95:5 to 90:10 over 7 min; t_R of (*R*)-**9a**: 7.8 min; t_R of (*S*)-**9a**: 9.1 min).

4.12. Confirmation of absolute stereochemistry. Reduction of bromides (*S*)-*23* and (*R*)-*17* to give (*S*)- and (*R*)-*24*

To a stirred 0.05 M solution of (*S*)-**23** (99% ee) or (*R*)-**17** (>99% ee) (1 equiv) in absolute THF at −78 °C was added a 1.29 M *t*-BuLi solution in pentane (1.2 equiv) dropwise under argon. The mixture was stirred at −78 °C for 15 min and then quenched by the dropwise addition of MeOH (2.4 mL/mmol of bromide). The mixture was allowed to reach room temperature and then the solvent was removed in vacuo and water was added to the residue. The product was extracted twice with ether, the organic layers were combined, and then dried over $MgSO_4$. The solvent was removed to give (*S*)-**24** (99%) and (*R*)-**24** (97%), respectively. We were unable to measure the ee of **24** by HPLC. However, metal–halogen exchange in (*S*)-**23** and in (*R*)-**17** was expected to proceed without racemization, since carbene complexes (*S*)-**6a** and (*R*)-**9a** can be been prepared without the loss of enantiomeric purity (see above). For (*S*)-**24**: $[\alpha]_D^{20}$ −247 (*c* 1, CH_2Cl_2) on 99% ee material. For (*R*)-**24**: $[\alpha]_D^{20}$ +248 (*c* 1, CH_2Cl_2) on >99% ee material.

4.13. Benzannulation reaction of carbene complex (*S*)-*6a* with pent-1-yne. Screening of reaction conditions

To a solution of (*S*)-**6a** (0.04 mmol, 20 mg) in dry solvent was added a 3-fold excess of pent-1-yne (8.16 mg, 0.12 mmol, 0.012 mL). The resulting solution was deoxygenated by the freeze–pump–thaw method (−196 °C/25 °C, three cycles). The flask was back-filled with argon at room temperature and sealed. The reaction was performed under the conditions indicated in Table 3. The red clear solution gradually changed to a dark mixture. The reaction mixture was opened to air, diluted with 1.5 mL of 40% EtOAc in hexane and stirred in the open flask for 24 h. The solvent was removed in vacuo and the crude product was filtered through a layer of silica gel (40% EtOAc in hexane). After the removal of the solvent, the diastereomeric ratio (dr) was determined from the crude product mixture by integration of the corresponding ^1H NMR signals (at least 48 scans). Then chromatographic separation of diastereomers was performed and the enantiomeric purity of **8a** (a*R*,7*S*) and **7a** (a*S*,7*S*) was determined by HPLC on a Chiralcel OD-H column. For **8a**: flow rate: 1 mL/min; hexane/*i*-PrOH 90:10 to 80:20 over 10 min; t_R of (a*R*,7*S*)-**8a**: 3.5 min; t_R of (a*S*,7*R*)-**8a**: 4.5 min. For **7a**: flow rate: 1 mL/min; hexane/*i*-PrOH 99:1 to 98:2 over 8 min; t_R of (a*R*,7*R*)-**7a**: 5.0 min; t_R of (a*S*,7*S*)-**7a**: 8.1 min. The results for the different solvents, temperatures, and concentrations are given in Table 3.

4.14. Benzannulation reaction of carbene complex (*S*)-*6a* with pent-1-yne in benzene and THF

The reaction of (*S*)-**6a** with pent-1-yne in benzene was performed according to the general procedure. Diastereomer (a*S*,7*S*)-**7a** was isolated in 46% yield and 72% ee (determined by HPLC (see conditions above)). Recrystallization from Et-C(O)Me/hexane mixture (8 h at 25 °C, 2 d at −20 °C) gave crystals of **7a** (22.5%, 8% ee). Enantiopure (a*S*,7*S*)-**7a** was isolated by evaporation of the mother liquor in vacuo (77.5%, >99% ee). The reaction of (*S*)-**6a** with pent-1-yne in THF was carried out at 35 °C for 60 h. The products were isolated according to the general procedure. The diastereomeric ratio (dr) **7a**:**8a** was 2.7:1 and the combined yield was 85%. Both diastereomers were formed without racemization (99% ee (HPLC)). For (a*R*,7*S*)-**8a**: $[\alpha]_D^{20}$ −83 (*c* 1, CH_2Cl_2) on 99% ee material. For (a*S*,7*S*)-**7a**: $[\alpha]_D^{20}$ −67 (*c* 1, CH_2Cl_2) on >99% ee material. CD ($[\theta]\times10^{-4}$ (nm), hexane) −1.2 (308), −5.3 (257), −2.0 (229), +10.9 (201).

4.15. Benzannulation reaction of carbene complex (*R*)-*9a* with 1-pentyne

The reaction of (*R*)-**9a** with pent-1-yne in benzene was performed according to the general procedure. Diastereomeric ratio (dr) **10a**:**11a** was 3.0:1 and the diastereomers (a*S*,7*R*)-**10a** and (a*R*,7*R*)-**11a** were isolated in 49% combined yield, both in >99% ee as determined by HPLC (Chiralcel OD-H column, flow rate: 1 mL/min; hexane/*i*-PrOH 99:1 to 98:2 over 8 min, then 98:2 to 95:5 over 7 min; t_R of (a*S*,7*R*)-**10a**: 5.2 min; t_R of (a*S*,7*S*)-**11a**: 7.1 min; t_R of (a*R*,7*S*)-**10a**: 7.5 min; t_R of (a*R*,7*R*)-**11a**: 10.2 min). For (a*S*,7*R*)-**10a**: $[\alpha]_D^{20}$ +64 (*c* 1, CH_2Cl_2); CD ($[\theta]\times10^{-4}$ (nm), hexane) −1.3 (307), −1.2 (257), −3.6 (230), +14.1 (200). For (a*R*,7*R*)-**11a**: $[\alpha]_D^{20}$ +104 (*c* 1, CH_2Cl_2); CD ($[\theta]\times10^{-4}$ (nm), hexane) +1.1 (306), +1.9 (255), +4.1 (228), −8.8 (201).

Acknowledgements

This work was supported by a grant from the National Institutes of Health (PHS-GM 33589).

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