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# Diastereoselective Multicomponent Cyclizations of Fischer Carbene Complexes, Lithium Enolates, and Allylmagnesium Bromide Leading to Highly Substituted Five- and Six-Membered Carbocycles

**José Barluenga,* Iván Pérez-Sánchez, Marcos G. Suero, Eduardo Rubio, and Josefa Flórez[a]**

**Abstract:** The one-pot sequential reaction of a chromium alkoxycarbene complex, a ketone or ester lithium enolate, and allylmagnesium bromide enabled the selective synthesis of novel diastereomerically pure pentasubstituted cyclopentanols or tetrasubstituted 1,4-cyclohexanediols, depending on the degree of substitution at the Cβ position of the enolate anion. A few exceptions have been encountered in which tetrasubstituted cyclopentanols or pentasubstituted 1,4-cyclohexanediols were selectively formed. The use of 2-iodoethoxycarbene complexes gave access to 1,2,4-cyclohexanetriols. These multicomponent-coupling reactions involved the formation of lithium alkylpentacarbonylchromates as key intermediates, which further evolved through intramolecular processes, such as insertion of an alkene, CO insertion or addition to a carbonyl group, and, moreover, could be trapped in intermolecular reactions with different electrophiles and styrene. The substitution pattern of the alkylchromate carbon chain has been proposed to control the nature of the annulation process.

**Keywords:** alkylchromates · carbene complexes · cyclization · enolates · multicomponent reactions

## Introduction

Group 6 Fischer carbene complexes have proved to be very efficient and extraordinarily versatile organometallic reagents for cyclization reactions that enable the synthesis of a wide range of cyclic-ring systems.[1] On the other hand, multicomponent reactions have attracted considerable interest owing to their efficiency as synthetic tools that assure a marked increase in molecular complexity and diversity and thereby an easy and rapid access to target molecules.[2] Here we report on a new multicomponent strategy for the selective synthesis of novel pentasubstituted cyclopentanols and tetrasubstituted 1,4-cyclohexanediols and which involves the sequential coupling reaction of an alkoxycarbene complex of chromium, a ketone or ester lithium enolate, and allylmagnesium bromide.[3]

The 1,2-addition reaction of metal enolates to Group 6 Fischer carbene complexes has been reported only with (aryl)(methoxy)- and (alkenyl)(methoxy)carbene complexes of chromium and tungsten. These carbene carbon additions generate initially anionic (1-methoxy-3-oxoalkyl)pentacarbonylmetalate species, which subsequently lead to different organic products depending on the reaction conditions and the nature of the reaction partners.[4] In the case of (aryl)(methoxy)carbene complexes the reactions of a W derivative with lithium or potassium enolates of ketones[5] and those of Cr derivatives with lithium enolates of α-haloesters[6] provided open-chain products after acid hydrolysis. Nucleophilic attack at the carbene carbon atom of (alkenyl)(methoxy)carbene complexes of Cr and W occurred when they were treated with methyl ketone lithium enolates. These experiments led to acyclic unsaturated ketones[5] when the reaction mixture was quenched at low temperature and to five-[7] or seven-membered[7a,c,d] carbocycles when the reaction was allowed to reach room temperature. The formation of the former acyclic unsaturated ketones has been explained through protonation at the remote allylic position of the lithium (allyl)pentacarbonylmetalate intermediates

[a] Prof. Dr. J. Barluenga, Dr. I. Pérez-Sánchez, M. G. Suero, Dr. E. Rubio, Dr. J. Flórez
Instituto Universitario de Química Organometálica "Enrique Moles"
Unidad Asociada al CSIC, Universidad de Oviedo
Julián Clavería 8, 33006 Oviedo (Spain)
Fax: (+34) 98-510-3450
E-mail: barluenga@uniovi.es

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generated in situ,[5] while the diastereoselective formation of the latter carbocycles involves intramolecular addition of these allylmetalate intermediates, which formally occurs with allylic transposition, to either the ketone carbonyl group or the β-carbon atom of an alkenyl ketone.[7] However, up to now, the nucleophilic addition of metal enolates to the carbene carbon atom of either alkynyl- or alkylcarbene complexes has not been reported.

In addition, the carbon-metal double bond reduction of alkoxycarbene complexes of Cr and W with *N*-methyl-1,4-dihydropyridine,[8] the analogous one-electron reduction of Cr derivatives with samarium diiodide in methanol,[9] the addition of sodium alkoxides, alkyllithium, and alkylmagnesium compounds,[8c] or the butyllithium addition to the carbene carbon atom of a Cr complex[10] afforded anionic (1-alkoxyalkyl)pentacarbonylmetalate intermediates which underwent in situ insertion of CO to give anionic (α-alkoxyacyl)tetracarbonylmetalate intermediates. These acyl chromate and tungstate complexes underwent intermolecular 1,4-addition to electron-deficient olefins,[8,9] intramolecular insertion of an alkene or alkyne,[8] intramolecular cyclopropanation of a carbon–carbon double bond,[8] or led to a more elaborated alkoxycarbene complex by treatment with methyl triflate.[10] Furthermore, alkyl- or (aryl)pentacarbonylchromate complexes, generated by addition of an organometallic compound (PhLi, $R_2Zn$) to $Cr(CO)_5L$ ($L=NMe_3$, THF), have been converted into (acyl)pentacarbonylchromate complexes in the presence of carbon monoxide (1 atm).[11] Further reaction of these latter intermediates with trimethyloxonium tetrafluoroborate led to chromium methoxycarbene complexes.[11b]

Other addition reactions of different types of both carbon nucleophiles or heteronucleophiles including hydride to the carbene carbon atom of Group 6 Fischer carbene complexes also produce (alkyl)pentacarbonylmetalate species.[1,12] These tetrahedral intermediates are known to undergo 1) protonation of the carbon–metal σ bond, as well as reaction with other electrophiles,[8c,13] 2) a dimerization process,[13a,14] 3) different elimination reactions leading to new carbene complexes[15] or nonmetal containing unsaturated products,[16] and 4) 1,2- or 1,3-shift of the $M(CO)_5$ fragment in the case of allyl and propargyl derivatives.[17]

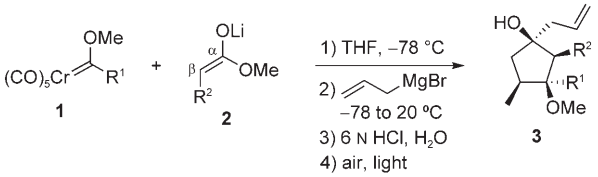
The results disclosed in this paper will provide evidence for new reaction patterns of both types of anionic intermediates: lithium (alkyl)pentacarbonylchromates and lithium (acyl)tetracarbonylchromates.

**Abstract in Spanish:** *La reacción secuencial de un complejo alcoxicarbeno de cromo con un enolato de litio de cetona o de éster y bromuro de alilmagnesio generó, con total diastereoselectividad, nuevos ciclopentanoles pentasustituidos o 1,4-ciclohexanodioles tetrasustituidos dependiendo del grado de sustitución del carbono en posición β del anión enolato. Algunas excepciones encontradas condujeron selectivamente a ciclopentanoles tetrasustituidos o 1,4-ciclohexanodioles pentasustituidos a partir de enolatos de litio no sustituidos o monosustituidos en el carbono β, respectivamente. La utilización de complejos 2-yodoetoxicarbeno permite obtener 1,2,4-ciclohexanotrioles. En estas reacciones de acoplamiento multicomponente se forman intermedios de tipo alquilpentacarbonilcromato de litio que posteriormente evolucionan a través de procesos intramoleculares como inserción de un alqueno, inserción de un ligando carbonilo (CO) o adición a un grupo carbonilo y que, además, experimentan reacciones intermoleculares con diferentes electrófilos y estireno. Se propone que el patrón de sustitución de la cadena carbonada del alquilcromato controla la naturaleza del proceso de anulación.*

## Results and Discussion

**Four-component synthesis of cyclopentanols 3. Formal [2+2+1] cyclization**: The successive reaction of chromium methoxycarbene complexes **1** with β-substituted ester lithium enolates **2** and then with allylmagnesium bromide under the reaction conditions summarized in Table 1 led, after hydrolysis with hydrochloric acid and decoordination of the metal center by exposure to air and light, to 1,2,3,3,4-pentasubstituted cyclopentanols **3**, which were formed in each case as a single diastereoisomer. Ester lithium enolates (*E*)-**2a** and **2b** (*Z*/*E*, 77:23) were prepared by deprotonation of methyl propionate and methyl phenylacetate, respectively, with lithium diisopropylamide (LDA) in THF.[18] The addition of these lithium enolates to carbene complexes **1** occurs at low temperature (-78 °C) and is an almost immediate reaction. The organomagnesium reagent was added at low temperature and then the reaction mixture was allowed to reach room temperature. 1-Allylcyclopentanols **3a**–**e** were successfully synthesized in a one-pot fashion from aryl- and heteroarylcarbene complexes **1a**, **1b** (Table 1, entries 1, 2,

Table 1. 1,2,3,3,4-Pentasubstituted cyclopentanols **3** prepared by one-pot four-component coupling of carbene complexes **1**, ester lithium enolates **2**, and allylmagnesium bromide.[a]




| Entry | Complex **1** | $R^1$ | Enolate **2** | $R^2$ | Product **3** | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | Me | **3a** | 84 |
| 2 | **1b** | 2-naphthyl | **2a** | Me | **3b** | 79 |
| 3 | **1c** | 2-furyl | **2a** | Me | **3c** | 73 |
| 4 | **1d** | $(CH_2)_4CH$[c] | **2a** | Me | **3d** | 87 |
| 5 | **1a** | Ph | **2b**[d] | Ph | **3e** | 88 |

[a] Reaction conditions: **2a**,**b** (1.2 equiv), −78 °C, 15 min; $CH_2=CHCH_2MgBr$ (2.5 equiv), −78 °C, 30 min and then 20 °C, 20 min. [b] Yield of isolated product is based on the corresponding carbene complex **1**. [c] Cyclopentyl. [d] Enolate **2b** is a mixture of diastereoisomers *Z*/*E* 77:23.

and 5), and **1c** (Table 1, entry 3), respectively, and even from alkylcarbene complex **1d** (Table 1, entry 4), which contains an acidic hydrogen atom at the tertiary center α to the carbene carbon atom. The experiment with lithium enolate **2b** (77:23 mixture of diastereoisomers *Z*/*E*) afforded cyclopentanol **3e** (Table 1, entry 5) with the same relative configuration as that of cyclopentanols **3a–d** prepared from diastereomerically pure *E* lithium enolate **2a**.

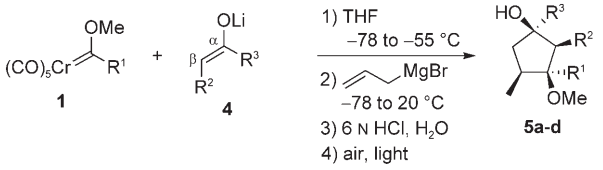
This sequential one-pot diastereoselective synthesis of cyclopentanols **3** with four contiguous stereogenic carbon centers represents the coupling of four reacting components with the formation of four new carbon–carbon (C–C) bonds. The cyclopentane ring of products **3** has been generated from the assembly of the carbene ligand as a one-carbon unit (carbene carbon atom) and the ester enolate and one of the allyl groups both as two-carbon synthons. Formally, the reaction shown in Table 1 can be considered as a $[2_E+2_A+1_C]$[19] cyclization process.

**Three-component synthesis of cyclopentanols 5. Formal [2+2+1] cyclization**: The analogous reaction carried out with (aryl)(methoxy)carbene complexes **1a**,**b**, β-substituted ketone lithium enolates **4a–c** and allylmagnesium bromide produced diastereoselectively 1,2,3,3,4-pentasubstituted cyclopentanols **5a–d** containing also four contiguous stereogenic carbon centers (Table 2). Ketone lithium enolates **4a** (*E*/*Z* ≈70:30) and (*E*)-**4b**,**c** were prepared by deprotonation of 3-pentanone, cyclohexanone, and cycloheptanone, respectively, with LDA/THF.[18a,20] The reaction of these ketone lithium enolates with carbene complexes **1** is a somewhat slower process for which an increase in the reaction temperature to -55 °C was required. The relative configuration of 1-alkylcyclopentanols **5** with a monocyclic **5a** (Table 2, entry 1) or a bicyclic structure **5b–d** (Table 2, entries 2–4) is identical to that of 1-allylcyclopentanols **3**. The overall process involves, in this case, the coupling of three reacting components and the formation of three new C–C bonds. Likewise, three separate carbon units have come together to form the cyclopentane core in a formal $[2_E+2_A+1_C]$[19] cyclization.

In contrast, when the same synthetic sequence was performed with the lithium enolate of cyclopentanone **4d**, carbene complex **1a** and allylmagnesium bromide, the formation of the corresponding bicyclic cyclopentanol of type **5** was never observed (Table 3). The experiment with enolate **4d**, generated from cyclopentanone and LDA, afforded 1-allylcyclopentanol **6** as a single diastereoisomer. The stereochemistry of the acyclic stereogenic center of product **6** has not been established. The structure of **6** indicates that the final ring closing has not occurred. To avoid the presence of the protic reagent diisopropylamine in the reaction mixture, which could be preventing the final cyclization step, the same experiment was accomplished with enolate **4d**, generated by treatment of 1-trimethylsilyloxycyclopentene with butyllithium, and by introducing a slight modification in the reaction conditions at low temperature with the Grignard reagent (−78 to −55 °C, 1 h instead of the standard conditions −78 °C, 30 min) to favor the ring closing. This reaction provided a mixture of compound **6** (major component) and bicyclic lactone **7** (minor component). Under these latter conditions (absence of diisopropylamine) compound **6** was isolated as a 3:1 mixture of diastereoisomers (different relative configuration at the acyclic stereogenic carbon center), while lactone **7** was formed as a unique diastereoisomer. These three compounds, the two diastereoisomers of **6** (**6** (major isomer), **6′** (minor isomer)) and **7**, were separated by flash-column chromatography. The butyrolactone ring of product **7** was formed by the gathering of three separated units in a formal $[3_E+1_C+1_{CO}]$[19] cyclization reaction.

**Five-component synthesis of 1,4-cyclohexanediols 8. Formal [2+2+1+1] cyclization**: The consecutive treatment of methoxycarbene complexes **1** with β-unsubstituted lithium eno-

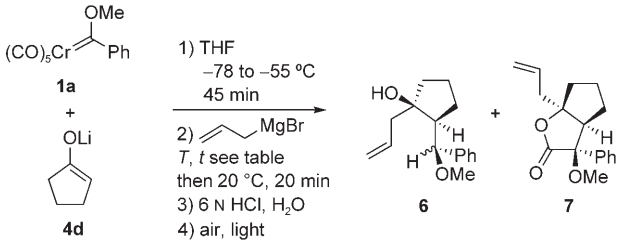
Table 2. 1,2,3,3,4-Pentasubstituted cyclopentanols **5a–d** prepared by one-pot three-component coupling of carbene complexes **1**, ketone lithium enolates **4**, and allylmagnesium bromide.[a]




| Entry | Complex **1** | $R^1$ | Enolate **4** | $R^2$ | $R^3$ | Product **5** | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **4a**[c] | Me | Et | **5a** | 80 |
| 2 | **1a** | Ph | **4b** | $(CH_2)_4$ | | **5b** | 72 |
| 3 | **1b** | 2-naphthyl | **4b** | $(CH_2)_4$ | | **5c** | 78 |
| 4 | **1b** | 2-naphthyl | **4c** | $(CH_2)_5$ | | **5d** | 63 |

[a] Reaction conditions: **4a–c** (1.2 equiv), −78 to −55 °C, 45 min; $CH_2$=$CHCH_2MgBr$ (1.5 equiv), −78 °C, 30 min and then 20 °C, 20 min. [b] Yield of isolated product is based on the corresponding carbene complex **1**. [c] Enolate **4a** is a mixture of diastereoisomers *E*/*Z*, approximately 70:30.

Table 3. Reactions with cyclopentanone lithium enolate **4d**.

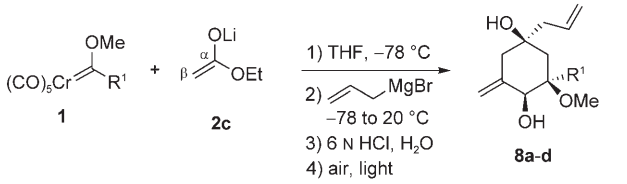



| **4d** prepared from | *T* [°C] | *t* | **6** | **7** |
|---|---|---|---|---|
| O + LDA | −78 °C | 30 min | 83 % | – |
| OTMS + BuLi | −78 to −55 °C | 1 h | 62 % 3:1 | 24 % |

late **2c** (prepared from EtOAc and LDA in THF) and then with allylmagnesium bromide, under the same reaction conditions described in Table 1, resulted in the diastereoselective formation of 1,3,3,5-tetrasubstituted 1,4-cyclohexanediols **8a–d** which contain three stereogenic carbon centers and an exocyclic carbon–carbon (C=C) double bond (Table 4). Aryl- (**1a**,**b**), heteroaryl- (**1e**), and also alkynyl-

Table 4. 1,3,3,5-Tetrasubstituted 1,4-cyclohexanediols **8a–d** prepared by one-pot five-component coupling of carbene complexes **1**, ester lithium enolate **2c**, and allylmagnesium Bromide.[a]

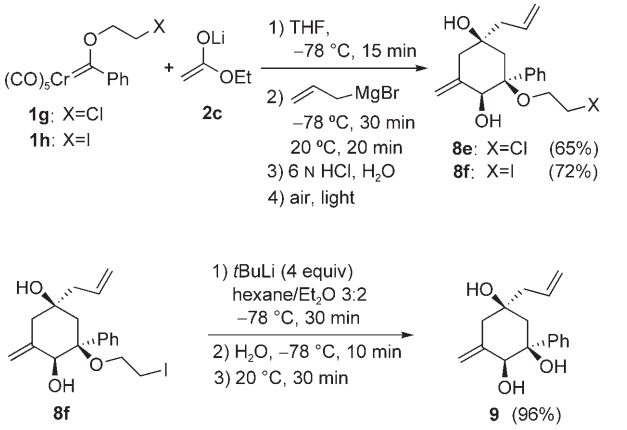



| Entry | Complex **1** | $R^1$ | Product **8** | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1a** | Ph | **8a** | 84 |
| 2 | **1b** | 2-naphthyl | **8b** | 79 |
| 3 | **1e** | 3-furyl | **8c** | 81 |
| 4 | **1f** | *t*BuC≡C | **8d** | 83 |

[a] Reaction conditions: **2c** (1.2 equiv), −78 °C, 15 min; $CH_2$=$CHCH_2MgBr$ (2.5 equiv), −78 °C, 30 min and then 20 °C, 20 min. [b] Yield of isolated product is based on the corresponding carbene complex **1**.

carbene (**1f**) complexes were successfully used as starting materials for the preparation of products **8a–d**. In the reactions with 3-furylcarbene complex **1e** and also with alkynylcarbene complex **1f** a selective addition of enolate **2c** to the carbene carbon was observed (Table 4, entries 3 and 4). 1-Allyl-1,4-cyclohexanediols **8** are the products derived from a formal $[2_E+2_A+1_C+1_{CO}]$[19] cyclization process in which five reacting components have been joined together with formation of five new C–C bonds.

The analogous sequential reaction of 2-haloethoxycarbene complexes **1g** (X=Cl) and **1h** (X=I) with lithium enolate **2c** and allylmagnesium bromide afforded the corresponding 1-allyl-1,4-cyclohexanediols **8e**,**f** as diastereomerically pure products (Scheme 1). These compounds **8e**,**f** enable easy

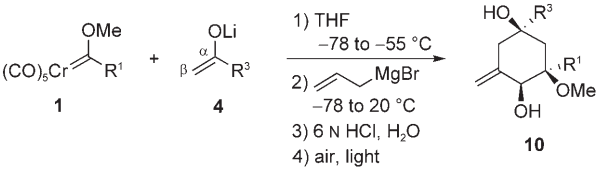



Scheme 1. Preparation of 1,2,4-cyclohexanetriol **9**.

access to cyclohexanetriols by ready conversion of the 2-haloethyl cyclohexyl ether moiety into the corresponding cyclohexanol unit. Thus, the 2-iodoethyl protecting group of compound **8f** was efficiently removed by treatment with *tert*-butyllithium (4 equiv) at −78 °C for 30 min by using a mixture of hexane/diethyl ether 3:2 as the solvent.[21] After hydrolysis, 1,2,4-cyclohexanetriol **9** was isolated in almost quantitative yield and as a single diastereoisomer (Scheme 1).[22,23]

**Four-component synthesis of 1,4-cyclohexanediols 10. Formal [2+2+1+1] cyclization**: β-Unsubstituted ketone lithium enolates **4** (prepared from the corresponding methyl ketone and LDA in THF) behaved in a similar way to enolate **2c** when they were treated with methoxycarbene complexes **1** and allylmagnesium bromide (Table 5). The reac-

Table 5. 1,3,3,5-Tetrasubstituted 1,4-cyclohexanediols **10** prepared by one-pot four-component coupling of carbene complexes **1**, ketone lithium enolates **4**, and allylmagnesium bromide.[a]




| Entry | Complex **1** | $R^1$ | Enolate **4** | $R^3$ | Product **10** | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **4e** | Me | **10a** | 82 |
| 2 | **1d** | $(CH_2)_4CH$[c] | **4e** | Me | **10b** | 87 |
| 3 | **1e** | 3-furyl | **4e** | Me | **10c** | 74 |
| 4 | **1a** | Ph | **4f** | *t*Bu | **10d** | 85 |
| 5 | **1e** | 3-furyl | **4f** | *t*Bu | **10e** | 78 |
| 6 | **1a** | Ph | **4g** | Ph | **10f** | 85 |
| 7 | **1b** | 2-naphthyl | **4g** | Ph | **10g** | 91 |
| 8 | **1e** | 3-furyl | **4g** | Ph | **10h** | 89 |

[a] Reaction conditions: **4e–g** (1.2 equiv), −78 to −55 °C, 45 min; $CH_2$=$CHCH_2MgBr$ (1.5 equiv), −78 °C, 30 min and then 20 °C, 20 min. [b] Yield of isolated product is based on the corresponding carbene complex **1**. [c] Cyclopentyl.

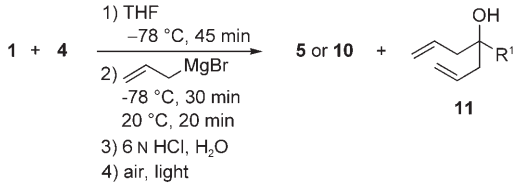
tions performed under identical experimental conditions to those reported in Table 2 provided diastereoselectively 1-alkyl- or 1-aryl-1,4-cyclohexanediols **10** with the same relative configuration as that of 1-allyl-1,4-cyclohexanediols **8** and which also incorporate the CH–OH unit inserted between the carbene carbon and the most substituted vinylic carbon of the allyl group. The six-membered carbocyclic framework of compounds **10** resulted from the coupling of four reacting components with the creation of four new C–C bonds through a formal $[2_E+2_A+1_C+1_{CO}]$[19] annulation process.

As pointed out above, in the reactions of ketone lithium enolates **4** with carbene complexes **1** it was necessary to raise the temperature of the reaction to −55 °C to get a complete addition reaction. Indeed, we observed that the experiments in which the temperature of the reaction step for carbene complex **1a** or **1b** with a β-substituted (**4a**,**b**) or β-unsubstituted (**4e**,**g**) ketone lithium enolate was main-

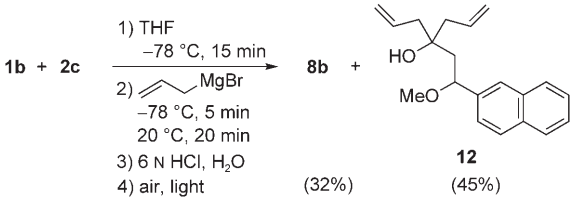
  

tained at −78 °C for 45 min (instead of 45 min between −78 and −55 °C) provided, after treatment with allylmagnesium bromide and further hydrolysis, the corresponding annulated product **5a**,**c** or **10a**,**g** accompanied by the appropriate tertiary alcohol **11a**,**b** as a minor product (Table 6; see for comparison Table 2 entries 1, 3 and Table 5, entries 1, 7). Compounds **5** or **10** and **11** were easily separated by column chromatography. The structure of bis(homoallylic) alcohols **11a** ($R^1$ = Ph) and **11b** ($R^1$ = 2-naphthyl), which do not contain the enolate framework, suggests that these derivatives were formed by direct addition of allylmagnesium bromide to the carbene carbon of the corresponding starting carbene complex **1a** ($R^1$ = Ph) or **1b** ($R^1$ = 2-naphthyl), which remained in the reaction mixture as a result of an incomplete addition of lithium ketone enolates **4** at −78 °C. In addition, we noticed that a shorter reaction time at low temperature in the second reaction step resulted in a low yield formation of the corresponding carbocyclic derivative. Thus, treatment of the reaction mixture obtained by addition of ethyl acetate lithium enolate (**2c**) to carbene complex **1b** with allylmagnesium bromide at −78 °C for only 5 min (instead of 30 min) and then at room temperature for 20 min furnished, after hydrolysis, cyclohexanediol **8b** (minor product) along with tertiary alcohol **12** (major product) (Table 6; see for comparison Table 4, entry 2). This open-chain bis(homoallylic) alcohol **12** incorporates in its structure the carbene ligand, the enolate framework, and two allyl units. These two compounds **8b** and **12** were separated by column chromatography.

Table 6. Secondary products observed under somewhat different reaction conditions.

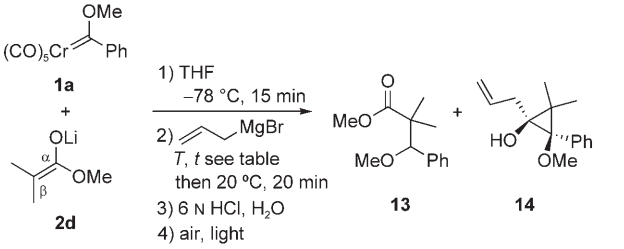



| 1 | 4 | 5 or 10 | Yield [%] | 11 | Yield [%] |
|---|---|---|---|---|---|
| **1a** | **4a** | **5a** | 57 | **11a** | 20 |
| **1b** | **4b** | **5c** | 62 | **11b** | 18 |
| **1a** | **4e** | **10a** | 65 | **11a** | 12 |
| **1b** | **4g** | **10g** | 61 | **11b** | 16 |




The behavior of a β,β-disubstituted lithium enolate in these cyclization processes was subsequently investigated. Table 7 summarizes the results obtained in the reaction of (methoxy)(phenyl)carbene complex **1a** with methyl isobutyrate lithium enolate (**2d**) and allylmagnesium bromide. Performance of this experiment under analogous reaction conditions to the above mentioned for reactions with other ester enolates yielded a mixture of β-methoxyester **13** (54%) and 1-allylcyclopropanol **14** (31%). This hexasubstituted-cyclopropane derivative was isolated as a unique diastereoisomer. A comparable result (mixture of **13** (52%) and **14** (35%)) was obtained in an experiment in which after the addition of allylmagnesium bromide the reaction was stirred for 1 h (instead of 30 min) while allowing the temperature (−78 °C) to rise to −55 °C (instead of keeping the reaction at −78 °C). A further experiment carried out under the latter reaction conditions, but with stirring of the reaction mixture between −78 and −55 °C for a longer period of time (6 h instead of 1 h) provided only cyclopropanol **14** (68%). Purification by column chromatography enabled the separation of compounds **13** and **14**. Cyclopropanol **14** is unstable and upon standing, even under nitrogen and with refrigeration (−3 °C), it slowly (15–20 d) decomposed to a mixture of carbonyl-containing products.[24] While methyl ester **13** is formally the α-alkylation product of methyl isobutyrate with the carbene ligand, cyclopropanol **14** is formally the product derived from a $[2_E+1_C]$ cycloaddition of the tetrasubstituted C=C double bond of an ester enolate to a Fischer carbene complex, occurring with concomitant allylation of the carbonyl group.

Table 7. Reactions with β,β-disubstituted lithium enolate **2d**.

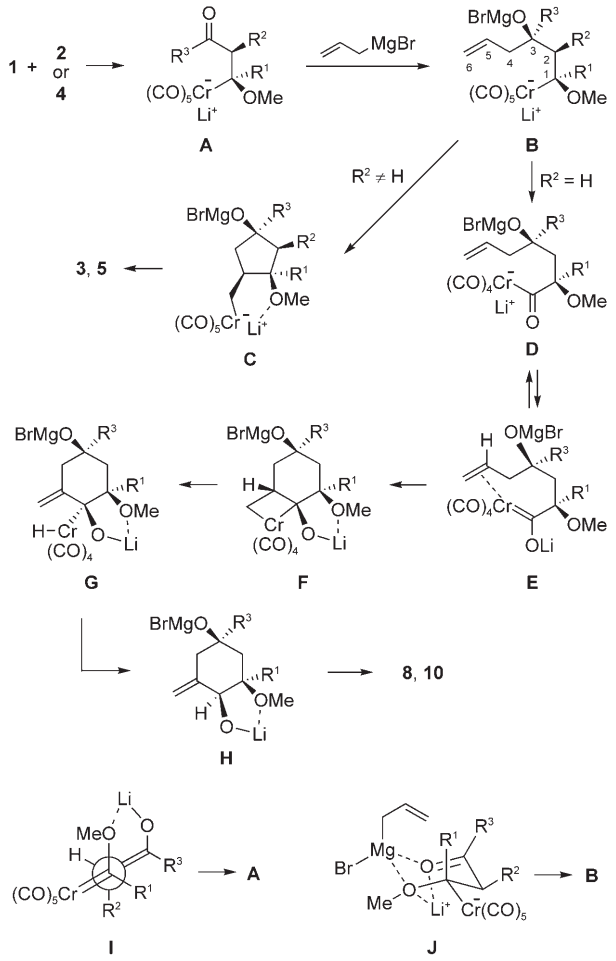



| T [°C] | t | Yield **13** [%] | Yield **14** [%] |
|---|---|---|---|
| −78 °C | 30 min | 54 | 31 |
| −78 to −55 °C | 1 h | 52 | 35 |
| −78 to −55 °C | 6 h | – | 68 |

The structure and relative stereochemistry of products **3**, **5a–d**, **6**, **7**, **8a–f**, and **9–14** were ascertained by 1D and 2D NMR spectroscopic experiments.[25] The latter studies were carried out with compounds **3b**,**e**, **5a**,**c**, **6**, **6′**, **7**, **8a–c**, **10d**, **12**, and **14**. Furthermore, a single-crystal X-ray analysis of **10a** ($R^1$ = Ph, $R^3$ = Me)[26] confirmed the structural assignment of 1,4-cyclohexanediols **8** and **10**.

**Mechanistic proposal and some exceptions**: The ring skeleton of cyclopentanols **3** and **5** combines the carbene ligand, the enolate framework, and two or one allyl groups, respectively, whereas that of 1,4-cyclohexanediols **8** and **10** incorporates, in addition, an one carbon unit "CH−OH" which seems to come from a carbonyl ligand. Accordingly, a reasonable mechanistic explanation for these multicomponent annulation reactions is depicted in Scheme 2. Initially the appropriate ester **2** ($R^3$ = OMe, OEt) or ketone **4** lithium enolate reacts at low temperature with carbene complex **1**,



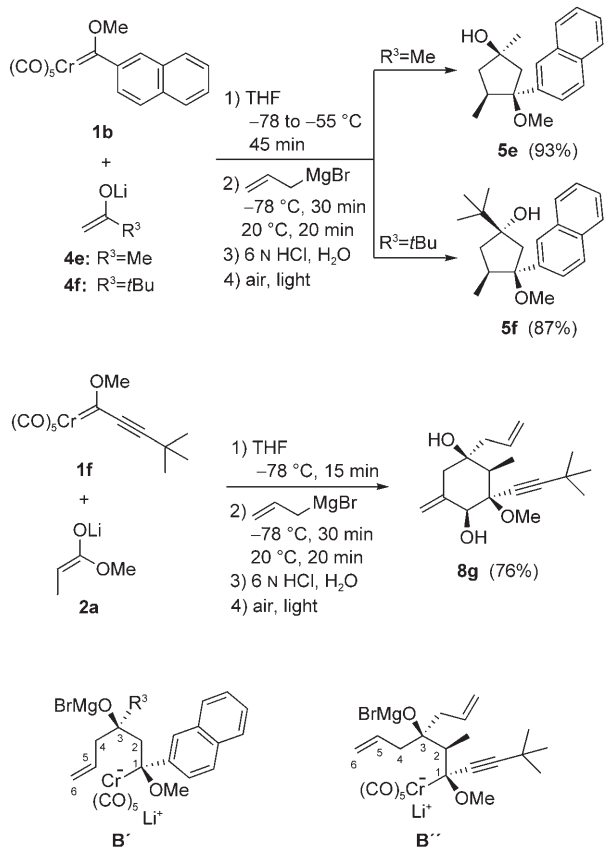
Scheme 2. Proposed mechanism for the formation of compounds **3**, **5**, **8**, and **10**.

undergoing a 1,2-addition to the carbene carbon that generates lithium (1-alkoxy-3-oxoalkyl)pentacarbonylchromate intermediate **A**. The subsequent addition at low temperature of the organomagnesium reagent to the corresponding ester or ketone functional group results in the formation of lithium 5-hexenylchromate intermediate **B**, for which the reactivity seems to depend on the degree of substitution at C2. Alkylchromate complexes **B** with an organic group at C2 ($R^2 \neq H$), arising from the reactions with β-substituted lithium enolates **2a**,**b** and **4a**–**c**, go through an intramolecular carbometalation reaction of the adequately positioned C5,C6 carbon–carbon double bond to give (cyclopentylmethyl)pentacarbonylchromate derivatives **C**.[27] Presumably, the substitution at C2 ($R^2 \neq H$) favors a more folded chain conformation of intermediate **B** that places the alkene and the σ C–Cr bond ends of the system in close proximity facilitating, therefore, the intramolecular alkene-insertion reaction into the C–Cr bond (**B**→**C**).[28] The final protonation of intermediates **C** provides cyclopentanols **3** ($R^3 = CH_2{=}CHCH_2$) and **5**. On the other hand, tetrahedral intermediates **B** formed in the reactions with β-unsubstituted lithium enolates **2c** and **4e**–**g** and which do not have a substituent at C2 ($R^2 = H$) presumably adopt a more extended chain conformation that puts the ends of the carbon chain further apart in space and, as a consequence, they undergo faster a carbon monoxide insertion into the C–Cr bond to give lithium (acyl)tetracarbonylchromate species **D**. These latter complexes **D** can be in equilibrium with the (tetracarbonyl)(lithiooxy)carbene complexes **E**; an intramolecular formal insertion of the carbene carbon atom into the secondary vinylic C–H bond of the allyl group might then lead to cyclized products **H**, which upon protonation finally furnish the observed 5-methylene-1,4-cyclohexanediols **8** ($R^3 = CH_2{=}CHCH_2$) and **10**.[29] This cyclization reaction (**E**→**H**) could involve a chromacyclobutane intermediate **F**, generated by a formal [2+2] cycloaddition of the π-systems from an initial ($\eta^2$-olefin)tetracarbonylcarbenechromium complex **E**, which subsequently undergoes a rearrangement to give hydridochromium complexes **G** and finally intermediates **H** through a process that may be regarded as a β-hydrogen elimination followed by a reductive elimination.[30]

The diastereoselectivity observed in the first reaction step: addition of the lithium enolate to the carbene carbon, can be explained in terms of approach topology **I** (Scheme 2), which assumes an aproximation of the reagents with an *anti* orientation of the acceptor (carbene complex) and donor (lithium enolate) π-systems and which is particularly favored in the case of *E* enolates by coordination of the lithium center to the oxygen atom of the carbene complex methoxy group. The diastereoisomer selectively formed in the second reaction step: addition of the allylmagnesium bromide to the ketone or ester carbonyl group, can be rationalized by a chelation-controlled transition state with a chairlike conformation in which the lithium and magnesium atoms are coordinated to both the carbonyl oxygen and the methoxy group oxygen as depicted in model **J** (Scheme 2). Addition of the nucleophile (organomagnesium) to the less-hindered face (back face of model **J**) of the carbonyl group accounts for the relative configuration of the C3 stereogenic center of intermediates **B**.[31] The diastereoselective formation of the last stereogenic carbon center generated in both annulation steps: **B**→**C** and **E**→**H** could be controlled by coordination of the lithium cation with the oxygen of the adjacent methoxy group which would finally favor the relative *cis* disposition of the methoxy group and the chromiomethyl or lithioxy group in intermediates **C** and **H**, respectively.

Notwithstanding, with regards to the general behavior revealed in these multicomponent cyclization reactions (Scheme 2), we have found some exceptions (Scheme 3) that involve formation of cyclopentanols (nonsubstituted at C2) from β-unsubstituted lithium enolates and generation of 1,4-cyclohexanediols (substituted at C2) from β-substituted lithium enolates. The reaction of 2-naphthylcarbene complex **1b** with lithium enolates **4e** ($R^3 = Me$) or **4f** ($R^3 = t$Bu) derived from acetone and *tert*-butyl methyl ketone, respectively, and then with allylmagnesium bromide under the standard reaction conditions developed for ketone enolates furnished 1,3,3,4-tetrasubstituted cyclopentanols **5e** and **5f**, isolated in each case as a unique diastereoisomer. Unexpected-



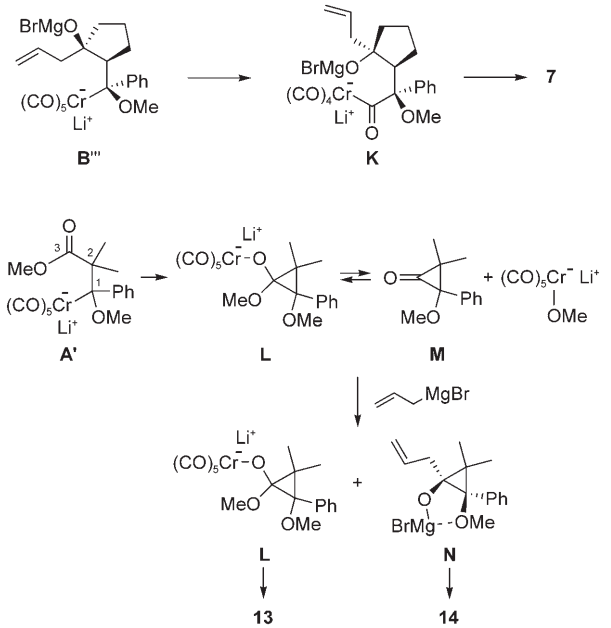

Scheme 3. Tetrasubstituted cyclopentanols and pentasubstituted 1,4-cyclohexanediols.

ly, the 1D and 2D NMR spectroscopic experiments[25] conducted with compounds **5e**,**f** ascertained that the relative arrangement of the *t*Bu and OH groups of 1-*tert*-butylcyclopentanol **5f** is just the opposite to the relative disposition of the Me and OH substituents of 1-methylcyclopentanol **5e** and also to that observed in the previously described pentasubstituted cyclopentanols **3** and **5a–d**. The structure and stereochemistry of compound **5f** was further confirmed by a X-ray structure analysis of a single crystal of **5f**.[32] In addition, the successive reaction of alkynylcarbene complex **1f** with methyl propionate lithium enolate (**2a**) and allylmagnesium bromide conducted under the standard reaction conditions established for ester enolates afforded 1,2,3,3,5-pentasubstituted-1,4-cyclohexanediol **8g** as a diastereomerically pure compound. The relative stereochemical configuration of cyclohexanediol **8g** has been assigned by analogy. A plausible explanation to rationalize the formation of products **5e**,**f** and **8g** could be found again in the conformational preference of the corresponding lithium 5-hexenylchromate intermediate **B** (Scheme 2). Although intermediates **B′** generated in the first reactions illustrated by Scheme 3 contain a less substituted carbon chain (unsubstituted at C2), they contain a bulky 2-naphthyl group at C1, which could be promoting greater folding in the chain conformation and therefore favoring the intramolecular carbometalation cyclization over the insertion of CO. While intermediate **B″** formed in the second experiment of Scheme 3 contains a more substituted carbon chain (Me at C2) but a linear alkynyl group at C1; the less steric requirements of this last substituent could be facilitating a more extended chain conformation and hence carbon monoxide insertion over the cyclization reaction.

Formation of product **12** (Table 6) results from the protonation of intermediate **B** ($R^1$=2-naphthyl, $R^2$=H, $R^3$=allyl) before the CO insertion and ring-closing reaction sequence has gone to completion due to a short reaction time at low temperature. This protonation reaction is promoted on increasing the temperature by the presence of diisopropylamine in the reaction mixture as will be established below.

Protonation of intermediate **B‴** (**B**: $R^1$=Ph, $R^2$, $R^3$=$(CH_2)_3$), which under the standard reaction conditions did not undergo the intramolecular carbometalation reaction probably due to an unfavorable geometry that finally could have to produce a strained *trans* fused bicyclo[3.3.0]octane ring system would account for the isolation of product **6** (Table 3). Formation of bicylic lactone **7**, which was obtained as a minor product when intermediate **B‴** was generated in the absence of diisopropylamine and furthermore kept for a longer time at a low temperature (see Table 3), involves evolution of alkylchromate **B‴** through a migratory insertion of carbon monoxide to give lithium (acyl)tetracarbonylchromate (**K**) which finally provides lactone **7** by intramolecular reaction of the bromomagnesium alkoxide with the acylchromate moiety presumably through an addition–elimination pathway (Scheme 4).

The results of Table 7 obtained in the experiments with β,β-disubstituted enolate **2d** can be explained by invoking the reaction pathway shown in Scheme 4. In this case, the

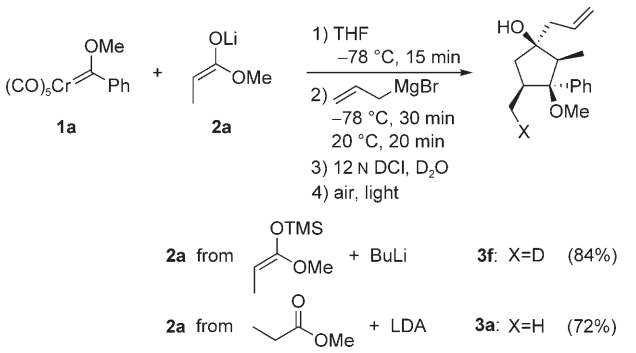



Scheme 4. Proposed mechanisms for the formation of compounds **7**, **13**, and **14**.

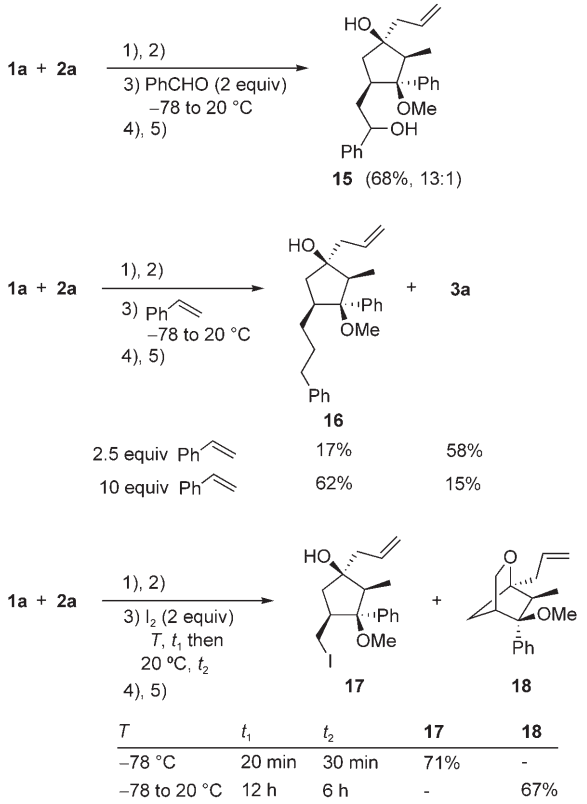
geminal disubstitution at C2 (*gem*-dialkyl effect)[28] of lithium 3-oxoalkylchromate intermediate **A′** enables it to adopt a favorable stereoelectronic approach to proceed immediately at low temperature through an intramolecular addition of the alkylchromate to the ester carbonyl group, yielding cyclopropane derivative **L**. This hemiketal metallic salt intermediate **L** can be in equilibrium with the corresponding tetrasubstituted cyclopropanone **M** formed by elimination of lithium methoxide-pentacarbonylchromium complex. When this reaction mixture is subsequently treated with the Grignard reagent, only intermediate **M** is able to undergo a diastereoselective carbonyl addition, whilst intermediate **L** remains unaltered. The diastereoselective formation of adduct **N** is most likely controlled by simultaneous coordination of the magnesium atom (allylmagnesium bromide) to both oxygen atoms of the carbonyl and methoxy groups of 2-methoxycyclopropanone **M**. The final hydrolysis of cyclopropane **L** occurs with ring opening and carbonyl regeneration leading to carboxylic ester **13**, whereas that of intermediate **N** affords tetrasubstituted cyclopropanol **14**. The transformation of hemiketal **L** to cyclopropanone **M** seems to be a slow process given that under the standard reaction conditions cyclopropanol **14** was isolated as the minor product, but formation of **14** was significantly improved by increasing the reaction time at low temperature (see Table 7) which seems to favor the conversion of intermediate **L** to **M**.

**Intermolecular trapping of lithium (alkyl)pentacarbonylchromates**: Direct evidence for the formation of cyclopentylmethylchromate intermediates **C** (Scheme 2) was attained by quenching the reaction with deuterium oxide and deuterated hydrochloric acid. The success of this experiment required that the presence of diisopropylamine in the reaction mixture be avoided, which at room temperature was found to promote protonation of the lithium alkylchromate C–Cr σ bond. As shown in Scheme 5 the reaction of carbene complex **1a** with lithium enolate **2a**, prepared from (*E*)-1-methoxy-1-trimethylsilyloxypropene and BuLi,[33] and then with allylmagnesium bromide afforded, after treatment with DCl-$D_2O$, deuterated cyclopentanol **3f**, whereas the same experiment carried out with lithium enolate **2a**, generated from methyl propionate and LDA, furnished the nondeuterium containing cyclopentanol **3a**.




Scheme 5. Formation of deuterated compound **3f** in the absence of $iPr_2NH$.

To obtain further insight into the reactivity of these alkylchromate organometallic reagents, we inspected the reaction of lithium cyclopentylmethylchromate intermediate **C′** ($R^1$ = Ph, $R^2$ = Me, $R^3$ = allyl) with other electrophiles and alkenes.[34] This derivative **C′** was prepared in the absence of diisopropylamine from **1a**, **2a**, and $CH_2$=$CHCH_2MgBr$ following the standard reaction conditions. The results of these experiments are gathered in Scheme 6. Quenching the reaction with benzaldehyde provided, after hydrolysis, benzyl alcohol derivative **15** as a 13:1 mixture of diastereoisomers due to the different relative configuration at the new stereogenic center formed by nucleophilic addition of the alkylchromate to the aldehyde carbonyl group. The major diastereoisomer was purified by column chromatography and its structure confirmed by 1D and 2D NMR spectroscopic experiments;[25] however, the stereochemistry of the exocyclic stereogenic center has not been established (first equation of Scheme 6). When the above mentioned reaction mixture was treated with styrene (2.5 equiv), product **16** resulting from the regioselective intermolecular carbometalation of this alkene with alkylchromate **C′** was isolated as a minor component along with the corresponding protonated cyclo-




Scheme 6. Synthesis of further functionalized pentasubstituted cyclopentanol derivatives. Reaction conditions: 1) **2a** (1.2 equiv), THF, –78 °C, 15 min; 2) $CH_2$=$CHCH_2MgBr$ (2.5 equiv), –78 °C, 30 min and then 20 °C, 20 min; 4) 6 N HCl, $H_2O$; 5) air, light. Enolate **2a** was prepared from the corresponding trimethylsilyl enol ether by treatment with BuLi.

pentanol **3a** as the major component (second equation of Scheme 6). The relative amounts of these reaction products **16** and **3a** were roughly inverted by adding a larger excess of styrene (10 equiv). Compounds **16** and **3a** were separated by column chromatography. A last experiment was conducted by using molecular iodine to quench the already mentioned reaction mixture before the hydrolysis step. This reagent ($I_2$) produced the electrophilic cleavage of the C($sp^3$)-Cr σ bond of intermediate **C′** resulting in the diastereoselective formation of 4-iodomethylcyclopentanol **17** or bicyclic ether **18** depending on the reaction time (third equation of Scheme 6). The iodine was added at low temperature (−78 °C) and then the reaction mixture was allowed to rise to room temperature. At short reaction times (30 min at 20 °C) cyclopentanol **17** was selectively formed, whereas longer reaction times (6 h at 20 °C) led to the selective formation of bicyclo[2.2.1]-2-oxaheptane **18** owing to the intramolecular nucleophilic displacement of the iodide ion by the magnesium alkoxide moiety. The structure and stereochemistry of compound **18** was confirmed by 1D and 2D NMR spectroscopic studies.[25]

## Conclusion

A novel one-pot and very efficient synthetic sequence that transforms three simple starting materials into structurally much more complex cyclic compounds has been developed. Singular and highly substituted cyclopentanols or 1,4-cyclohexanediols as single diastereoisomers are readily accessible from alkoxycarbene complexes, ketone, or ester lithium enolates and allylmagnesium bromide by mainly an appropriate choice of lithium enolate. Lithium alkylpentacarbonylchromates are formed as key intermediates in these coupling reactions. The nature and substitution pattern of the alkyl carbon chain of these intermediates seems to control the size of the ring and the final intermolecular trapping of intermediates of this type with different reagents led to further functionalized cyclopentanol derivatives. These formal [2+2+1] or [2+2+1+1] cyclizations processes involve the selective sequential formation of up to five new C–C bonds and up to four contiguous stereogenic centers. Additionally, the 1,2-addition reaction of lithium enolates to the carbene carbon of alkyl- and alkynylcarbene complexes is reported for the first time.

## Experimental Section

**General procedure for the synthesis of compounds 3, 5, 8, and 10**: Ester enolates **2** or ketone enolates **4** were prepared by treatment of a solution of the corresponding ester or ketone (1.1 mmol) in THF (2 mL) with lithium diisopropylamide (1.2 mmol, 1.2 M in THF, 1 mL) at −78 °C for 1 h. The resulting solution of enolate **2** or **4** was then added at −78 °C to a solution of the corresponding carbene complex **1a–h** (1 mmol) in THF (15 mL). This mixture was stirred for 15 min at −78 °C in the experiments with ester lithium enolates **2**, and in the reactions with ketone lithium enolates **4** the mixture was stirred for 45 min while the temperature was allowed to reach −55 °C. The initial dark red (**1a–c,e–h**) or orange (**1d**) solution of the starting carbene complex turned yellow instantaneously at −78 °C (experiments with ester enolates **2**) or gradually from −78 to −55 °C (experiments with ketone enolates **4**). Allylmagnesium bromide (2.5 mmol, 1 M in $Et_2O$, 2.5 mL (experiments with ester enolates **2**) or 1.5 mmol, 1 M in $Et_2O$, 1.5 mL (experiments with ketone enolates **4**)) was then added at −78 °C. After the reaction mixture had been stirred for 30 min at −78 °C, it was warmed to room temperature and stirred for a further 20 min period. After this time, the mixture was quenched with $H_2O$ (10 mL) and neutralized with HCl (ca. 6 N, 2 mL). The resulting mixture was diluted with hexane/ethyl acetate 5:1 (100 mL) and subjected to air oxidation under direct sunlight. After 1 d, the suspension was filtered through Celite and extracted with ethyl acetate (3×15 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The crude products were purified by column chromatography to give the corresponding cyclopentanol **3a–e** or **5a–f** (silica gel, hexane/EtOAc 9:1, hexane/$CH_2Cl_2$ 3:2, or hexane/$Et_2O$ 3:1) or 1,4-cyclohexanediol **8a–g** or **10a–h** (silica gel, hexane/EtOAc 3:1, hexane/EtOAc 1:1, or $CH_2Cl_2$/$Et_2O$ 10:1) as pure compounds and each one as a single diastereoisomer. Yields are listed in Tables 1, 2, 4, 5, and Schemes 1 and 3.

**(1*R**,2*R**,3*S**,4*S**)-1-Allyl-3-(2-furyl)-3-methoxy-2,4-dimethylcyclopentanol (3c)**: Colorless oil; $R_f$=0.18 (hexane/$Et_2O$ 3:1); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$= 0.67 (d, $J$=7.4 Hz, 3H), 1.00 (d, $J$=7.1 Hz, 3H), 1.54 (dd, $J$=14.2, 6.6 Hz, 1H), 2.20–2.31 (m, 3H), 2.43–2.55 (m with dd at 2.47, $J$=13.7, 7.1 Hz, 2H), 3.35 (s, 3H), 3.45 (s, 1H), 5.16 (brs, 1H), 5.21 (brs, 1H), 5.85–5.99 (m, 1H), 6.24 (d, $J$=3.1 Hz, 1H), 6.36 (apparent t, $J$=1.6 Hz, 1H), 7.39 ppm (brs, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$= 6.3 ($CH_3$), 18.8 ($CH_3$), 43.5 ($CH_2$), 44.9 (CH), 46.4 ($CH_2$), 52.1 (CH), 55.4 ($CH_3$), 81.4 (C), 85.2 (C), 106.1 (CH), 110.0 (CH), 118.6 ($CH_2$), 133.8 (CH), 141.5 (CH), 156.2 ppm (C); LRMS (70 eV, EI): *m/z* (%): 218 (31) [$M-CH_3OH$]$^+$, 193 (20), 177 (18), 127 (44), 124 (100), 123 (33), 95 (49), 69 (49); HRMS (70 eV, EI): calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1297 [$M-CH_3OH$]$^+$.

**(1*R**,2*R**,3*S**,4*S**)-1-Ethyl-3-methoxy-2,4-dimethyl-3-phenylcyclopentanol (5a)**: Colorless oil; $R_f$=0.32 (hexane/EtOAc 9:1); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$= 0.96 (t, $J$=7.4 Hz, 3H), 0.98 (d, $J$=7.1 Hz, 3H), 1.10 (d, $J$=7.1 Hz, 3H), 1.32–1.44 (m, 1H), 1.65–1.77 (m, 2H), 1.89 (q, $J$=7.1 Hz, 1H), 2.14–2.27 (m, 1H), 2.36 (dd, $J$=13.5, 9.4 Hz, 1H), 3.29 (s, 3H), 3.38 (brs, 1H), 7.26–7.42 ppm (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$= 7.4 ($CH_3$), 8.5 ($CH_3$), 14.4 ($CH_3$), 31.2 ($CH_2$), 42.5 (CH), 45.7 ($CH_2$), 52.1 (CH), 55.3 ($CH_3$), 80.1 (C), 91.3 (C), 126.9 (CH), 127.0 (2CH), 128.1 (2CH), 139.7 ppm (C); LRMS (70 eV, EI): *m/z* (%): 230 (41) [$M-H_2O$]$^+$, 216 (54), 159 (47), 148 (41), 137 (100), 134 (40), 117 (39), 105 (69), 91 (26), 76 (27); HRMS (70 eV, EI): calcd for $C_{16}H_{22}O$: 230.1671; found: 230.1667 [$M-H_2O$]$^+$.

**(1*S**,3*R**,4*S**)-1-(1,1-Dimethylethyl)-3-methoxy-4-methyl-3-(2-naphthyl)cyclopentanol (5f)**: White solid; m.p. 97–99 °C; $R_f$=0.18 (hexane/$CH_2Cl_2$ 3:2); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.92 (d, $J$=6.8 Hz, 3H), 1.02 (s, 1H), 1.06 (s, 9H), 1.59 (dd, $J$=12.0, 5.9 Hz, 1H), 2.07 (t, $J$=12.8 Hz, 1H), 2.29 (d, $J$=15.6 Hz, 1H), 2.40 (apparent septet, $J$=6.5 Hz, 1H), 2.67 (d, $J$=15.6 Hz, 1H), 3.20 (s, 3H), 7.44–7.50 (m, 2H), 7.61 (d, $J$=7.3 Hz, 1H), 7.80–7.86 ppm (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$= 10.9 ($CH_3$), 25.6 (3$CH_3$), 36.9 (C), 42.9 ($CH_2$), 43.4 ($CH_2$), 47.2 (CH), 51.2 ($CH_3$), 85.6 (C), 89.0 (C), 124.8 (CH), 125.1 (CH), 125.5 (CH), 125.8 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH), 132.2 (C), 133.1 (C), 141.2 ppm (C); LRMS (FAB+): *m/z* (%): 313 (6) [$M$+H]$^+$, 312 (16) [$M$]$^+$, 281 (22), 264 (26), 263 (100), 255 (27), 223 (35), 221 (38), 207 (52), 195 (40), 181 (39), 179 (31), 167 (33), 165 (43), 155 (96); HRMS (FAB+): calcd for $C_{21}H_{29}O_2$: 313.2168; found: 313.2156 [$M$+H]$^+$; elemental analysis calcd (%) for $C_{21}H_{28}O_2$: C 80.73, H 9.03; found: C 80.52, H 8.96.

**(1*R**,3*S**,4*S**)-1-Allyl-3-(3-furyl)-3-methoxy-5-methylene-1,4-cyclohexanediol (8c)**: White solid; m.p. 144–146 °C; $R_f$=0.32 (hexane/EtOAc 1:1); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=2.21 (d, $J$=17.9 Hz, 1H), 2.28–2.31 (m, 2H), 2.38–2.43 (m, 3H), 2.49 (d, $J$=10.0 Hz, 1H), 3.15 (s, 3H), 3.69 (s, 1H), 4.05 (brd, $J$=10.0 Hz, 1H), 5.10–5.13 (m, 2H), 5.16 (apparent d, $J$=1.0 Hz, 1H), 5.36 (apparent d, $J$=1.0 Hz, 1H), 5.87–6.01 (m, 1H),

6.53 (s, 1H), 7.42 (brs, 1H), 7.49 ppm (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 38.9 ($CH_2$), 45.7 ($CH_2$), 46.3 ($CH_2$), 51.7 ($CH_3$), 71.9 (C), 77.6 (CH), 78.8 (C), 110.2 (CH), 112.2 ($CH_2$), 118.2 ($CH_2$), 125.9 (C), 133.4 (CH), 140.7 (CH), 142.8 (CH), 143.3 ppm (C); LRMS (70 eV, EI): *m/z* (%): 264 (8) $[M]^+$, 214 (28), 173 (58), 145 (100), 125 (45), 117 (34), 95 (33); HRMS (70 eV, EI): calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1367 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found: C 68.27, H 7.74.

**(1*R**,2*R**,3*S**,4*S**)-1-Allyl-3-(3,3-dimethyl-1-butynyl)-3-methoxy-2-methyl-5-methylene-1,4-cyclohexanediol (8g)**: Pale yellow oil; $R_f$ = 0.15 (hexane/EtOAc 3:1); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.23 (d, $J$ = 7.1 Hz, 3H), 1.29 (s, 9H), 1.72 (q, $J$ = 7.1 Hz, 1H), 2.24 (brs, 1H), 2.26 (brs, 1H), 2.30 (brs, 1H), 2.33–2.40 (m, 2H), 3.53 (s, 3H), 3.96 (s, 1H), 4.07 (brs, 1H), 5.05 (brs, 1H), 5.08 (brs, 1H), 5.13 (d, $J$ = 3.4 Hz, 1H), 5.27 (brs, 1H), 5.71–5.85 ppm (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 9.6 ($CH_3$), 27.5 (C), 30.8 (3$CH_3$), 44.0 ($CH_2$), 45.0 (CH), 45.5 ($CH_2$), 52.7 ($CH_3$), 74.1 (C), 75.0 (C), 79.1 (CH), 83.1 (C), 98.7 (C), 110.8 ($CH_2$), 116.2 ($CH_2$), 133.5 (CH), 141.3 ppm (C); LRMS (70 eV, EI): *m/z* (%): 292 (0.4) $[M]^+$, 260 (36) $[M-CH_3OH]^+$, 245 (41), 219 (31), 203 (58), 191 (59), 173 (37), 159 (48), 153 (66), 152 (75), 137 (47), 109 (94), 69 (100); HRMS (70 eV, EI): calcd for $C_{18}H_{28}O_3$: 292.2038 $[M]^+$; found: 292.2047.

**(1*R**,3*S**,4*S**)-3-Cyclopentyl-3-methoxy-1-methyl-5-methylene-1,4-cyclohexanediol (10b)**: Colorless solid; m.p. 128–130 °C; $R_f$ = 0.20 (hexane/EtOAc 3:1); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.20 (s, 3H), 1.40–1.67 (m, 8H), 1.75–1.81 (m, 1H), 1.93 (dd, $J$ = 14.7, 3.0 Hz, 1H), 2.15 (brd, $J$ = 13.4 Hz, 1H), 2.25 (brd, $J$ = 6.5 Hz, 1H), 2.39 (dd, $J$ = 13.4, 3.1 Hz, 1H), 2.55 (quintet, $J$ = 8.6 Hz, 1H), 3.34 (s, 3H), 4.07 (brs, 1H), 4.22 (s, 1H), 5.02 (apparent s, 1H), 5.20 ppm (apparent s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 25.3 ($CH_2$), 25.8 ($CH_2$), 27.0 ($CH_2$), 28.7 ($CH_2$), 29.2 ($CH_3$), 38.6 ($CH_2$), 42.1 (CH), 47.8 ($CH_2$), 51.1 ($CH_3$), 70.6 (C), 76.2 (CH), 83.0 (C), 109.9 ($CH_2$), 145.2 ppm (C); LRMS (70 eV, EI): *m/z* (%): 241 (0.3) $[M+H]^+$, 240 (0.5) $[M]^+$, 208 (28), 190 (46), 171 (29), 169 (42), 153 (44), 150 (30), 147 (23), 137 (55), 127 (38), 121 (31), 111 (42), 97 (37), 95 (49), 85 (31), 71 (100), 69 (40); HRMS (70 eV, EI): calcd for $C_{14}H_{24}O_3$: 240.1725 $[M]^+$; found: 240.1728; elemental analysis calcd (%) for $C_{14}H_{24}O_3$: C 69.96, H 10.07; found: C 69.70, H 10.18.

**(1*R**,2*R**,3*S**,4*S**)-1-Allyl-4-deuteriomethyl-3-methoxy-2-methyl-3-phenylcyclopentanol (3f)**: Butyllithium (1.1 mmol, 1.6 M in hexanes, 0.69 mL) was added to a solution of (*E*)-1-methoxy-1-trimethylsilyloxypropene (1.1 mmol, 176 mg) in THF (2 mL) at −78 °C.[33] The mixture was stirred for 15 min at -78 °C and then for 15 min at 0 °C. The resulting solution of enolate **2a** was then added at −78 °C to a solution of carbene complex **1a** (1 mmol, 312 mg) in THF (15 mL). After 15 min at −78 °C, allylmagnesium bromide (2.5 mmol, 1 M in $Et_2O$, 2.5 mL) was added. The resulting reaction mixture was stirred for 30 min at −78 °C and was then warmed to room temperature and stirred for a further 20 min period. After this time, the mixture was quenched with $D_2O$ (10 mL) and neutralized with DCl (solution in $D_2O$, ca. 12 N, 1 mL). The reaction workup was carried out as indicated above (general procedure). Column chromatography on silica gel (hexane/EtOAc 9:1) afforded cyclopentanol **3f** as a single diastereoisomer (0.84 mmol, 219 mg, 84%). Colorless oil; $R_f$ = 0.36 (hexane/EtOAc 9:1); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.00 (d, $J$ = 7.1 Hz, 3H), 1.07 (brd, $J$ = 7.1 Hz, 2H), 1.69 (dd, $J$ = 13.9, 10.5 Hz, 1H), 1.91 (q, $J$ = 7.1 Hz, 1H), 2.13–2.22 (m, 2H), 2.38–2.47 (m, 2H), 3.29 (s, 3H), 3.38 (brs, 1H), 5.09–5.15 (m, 2H), 5.83–5.97 (m, 1H), 7.29–7.42 ppm (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 7.3 ($CH_3$), 14.1 (t, $^1J$(C,D) = 19.5 Hz, $CH_2D$), 42.4 (CH), 43.2 ($CH_2$), 46.0 ($CH_2$), 52.0 (CH), 55.3 ($CH_3$), 79.4 (C), 91.2 (C), 117.7 ($CH_2$), 126.9 (CH), 127.0 (2CH), 128.1 (2CH), 134.6 (CH), 139.5 ppm (C); LRMS (70 eV, EI): *m/z* (%): 243 (13) $[M-H_2O]^+$, 229 (13), 214 (14), 188 (28), 149 (44), 146 (50), 137 (100), 117 (35), 105 (44); HRMS (70 eV, EI): calcd for $C_{17}H_{21}DO$ $[M-H_2O]^+$: 243.1733; found: 243.1730.

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