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# Solvent-Controlled Diastereoselective Synthesis of Cyclopentane Derivatives by a [3 + 2] Cyclization Reaction of α,β-Disubstituted (Alkenyl)(methoxy)carbene Complexes with Methyl Ketone Lithium Enolates

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***Abstract:*** Reaction of α,β-unsaturated methoxycarbene complexes **1** and **11** with methyl ketone lithium enolates **2** leads to the corresponding five-membered carbocyclic compounds **4** or ***diast*-4** and **12**. The influence of the solvent and/or cosolvent (PMDTA), which turned out to be crucial to direct the reaction to **4** or ***diast*-4**, is studied, and a tentative mechanism according to these facts is proposed. In addition, the reaction of carbene complex **1a** with alkynyl methyl ketone lithium enolates can be directed to the formal [3 + 2] or [4 + 1] cyclization products by a slight variation of the reaction conditions. Finally, consecutive three-component coupling reactions with carbene complex **1a**, lithium enolates **2**, and aldehydes **18** to give, in a diastereoselective way, hydroxy carbonyl compounds **19** and tricyclic polyethers **20** are presented.

## Introduction

The design of new strategies for the selective synthesis of five-membered carbocycles continues to be of great interest for organic chemists[1] due to the importance of this skeleton as a part of biologically relevant compounds.[2] The Pauson−Khand reaction constitutes, among the organometallic methods, one of the most important processes for the easy construction of substituted cyclopentenones.[3] Moreover, Fischer carbene complexes, which have turned out to be extremely useful tools for synthesizing a wide variety of complex molecules,[4] have been revealed as a solid alternative for the preparation of five-membered rings.[5] In particular, stabilized group 6 α,β-unsaturated carbene complexes are recognized as valuable C3 building blocks for formal [3 + 2] carbo- and heterocyclization reactions. Thus, reactions with alkynes,[6] electron-poor alkenes,[7] siloxy-substituted 1,3-dienes,[8] 1-amino-1-aza-1,3-dienes,[9] enamines,[10] and isonitriles[11] give rise to functionalized five-membered carbocycles, while the reaction with imines leads to pyrrol derivatives.[12] Moreover, lithium enolates add to α,β-unsaturated carbene complexes in a Michael fashion,[13] and at the beginning of our investigations in this field only one example had been reported in which the lithium enolate of acetone reacted with vinylcarbene complexes through 1,2-nucleophilic attack to furnish α,β-unsaturated ketones.[13a] In this context, we have

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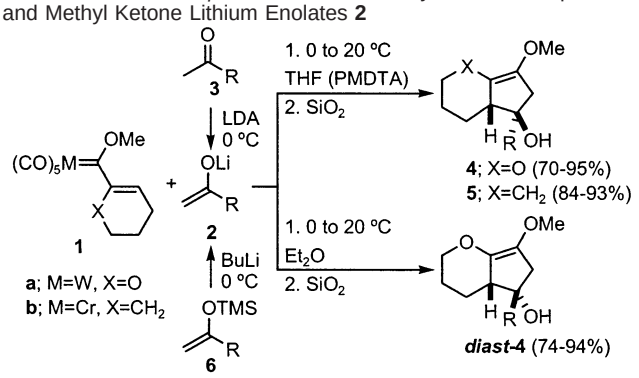
***Scheme 1.*** Diastereoselective Formation of Five-Membered Rings **4** and ***diast*-4** from α,β-Unsaturated Methoxycarbene Complexes **1** and Methyl Ketone Lithium Enolates **2**




recently[14] developed a novel [3 + 2] cyclization reaction of alkenyl Fischer carbene complexes with lithium enolate of methyl ketones, leading to five-membered carbocyclic rings, and, in this paper, we would like to present the scope of this transformation and the influence of the solvent and or cosolvent on the diastereoselectivity of the reaction. As a complementary reaction pattern, we also report a three-component sequential reaction between the α,β-unsaturated carbene complex, the methyl ketone lithium enolate, and an aromatic aldehyde to afford hydroxyketone derivatives in a diastereoselective way.

## Results and Discussion

The treatment of alkenylcarbene pentacarbonyl complexes **1** with methyl ketone lithium enolates **2**, generated by deprotonation of ketones **3** with lithium diisopropyl amide (LDA) at 0 °C, in THF at temperatures from 0 °C to room temperature led, after hydrolysis and purification by column chromatography on deactivated silica gel, to cyclopentenol derivatives **4** and **5** in good yields (Scheme 1 and Table 1). Better results were obtained when the transformation was carried out under the same reaction conditions but using lithium enolates **2** generated by treatment of silyl enol ethers **6** with butyllithium at temperatures from 0 °C to room temperature. The diastereoselectivity found in the reaction of carbene complex **1a** with lithium enolates **2** to give cyclopentenol derivatives **4** was very good in almost all of the cases. However, this diastereoselectivity was observed to strongly depend on the substituent R on the lithium enolate **2**. Thus, when the substituent R on lithium enolates **2** is an alkyl group, the diastereoselectivity of **4** varies according to the bulkiness of the R group. For R = Me, cyclopentenol derivative **4a** was obtained in good yield and as a single diastereoisomer (Table 1, entry 1). Similar results were obtained when R is a primary alkyl group; thus, starting from lithium enolate **2b** (R = $^i$Bu), cyclopentenol derivative **4b** is obtained in 77% yield and with 82% de (Table 1, entry 2). This result could be improved to 90% de by using *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA) as cosolvent, or >95% de if a mixture of $Et_2O$/PMDTA was used (Table 1, entries 3 and 4). A different result was found starting from lithium enolate **2c** in which the R group is a secondary alkyl group (R = $^i$Pr); in this case, an equimolecular mixture of **4c** and ***diast*-4c** was formed (Table 1, entry 5). However, the use of PMDTA was crucial, resulting in a considerable increase in the diastereoselectivity of the reaction. Thus, **4c** was generated in 63 or 78% de when the reaction was carried out either in THF or in $Et_2O$ and using PMDTA as cosolvent (Table 1, entries 6 and 7). Furthermore, when lithium enolate **2d** (R = $^t$Bu) was reacted, ***diast*-4d** was exclusively generated, both in the absence and in the presence of PMDTA (Table 1, entry 8). Reaction of lithium enolates **2e**−**g** derived from aryl or heteroaryl methyl ketones led to a mixture of compounds **4e**−**g** and ***diast*-4e**−**g** in an equimolecular ratio or with a slight predominance of **4** (Table 1, entries 9, 11, 14). However, addition of 3 equiv of PMDTA to the THF or $Et_2O$ solution gave rise to the formation of **4e**−**g** as the major diastereoisomer (Table 1, entries 10, 12, 13, 15). When lithium enolates **2h**−**m**, in which R is an alkenyl moiety, were used, products **4h**−**m** were obtained with good yields, but the diastereoselectivity found depended on the substitution pattern in the carbon−carbon double bond. Thus, while the reaction of **1a** with β-substituted lithium alkenolates **2h**−**j** afforded the corresponding cyclopentenol derivatives **4h**−**j** in good yields and with diastereoselectivities higher than 90% (Table 1, entries 16−18), the β,β-disubstituted lithium alkenolate **2k** afforded **4k** with a poor 25% de. This diastereoselectivity could be increased to 90% when the reaction was carried out in the presence of PMDTA (Table 1, entries 19 and 20). However, when cycloalkenyl-substituted lithium alkenolates **2l**,**m** were reacted, ***diast*-4l**,**m** were exclusively generated, and no changes were observed when PMDTA was added (Table 1, entries 21 and 22). It is interesting to note that in the reactions attempted using lithium enolates derived from alkenyl methyl ketones, the formation of the expected seven-membered carbocyclic compound was not observed.[14] Finally, products **4n**−**p** were exclusively obtained when lithium enolates **2n**−**p** derived from alkynyl methyl ketones were used as starting materials, and only lithium enolate **2o** required the presence of PMDTA to form **4o** as a sole diastereoisomer (Table 1, entries 23−26). In addition, a single diastereoisomer of **5** was obtained starting from carbene complex **1b** and lithium enolates **2a**,**e**,**h**,**n** derived from methyl, phenyl, alkenyl, and alkynyl methyl ketones (entries 27−30).

On the contrary, when the reaction of carbene complex **1a** and lithium enolates **2**, formed from silyl enol ethers **6**, was carried out under the same reaction conditions but using diethyl ether as solvent, ***diast*-4** was obtained in good yields and as a single diastereoisomer in each case independent of the nature of the R substituent of the lithium enolate (Table 1, entries 31−45). Only in the case of the reaction of lithium enolate **2a**, derived from acetone, was an equimolecular mixture of the easily separated compounds **4a** and ***diast*-4a** generated (Table 1, entry 31). The other exceptional cases are those starting from β-lithium arylalkenolates **2h**,**i**. Here, the corresponding cyclopentenol derivatives ***diast*-4h**,**i** were obtained with lower de values (79 and 82%, respectively) (Table 1, entries 38 and 39). The structures and relative configurations of the new stereogenic centers of **4** and ***diast*-4** were unequivocally determined by two-

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***Table 1.*** Solvent Effect in the Synthesis of Cyclopentenol Derivatives **4** and ***diast*-4** from Carbene Complexes **1** and Methyl Ketone Lithium Enolates **2**

| entry | carbene complex | X | enolate | R | solvent (cosolvent)[a] | product | yield (%)[b] | de (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | O | **2a** | Me | THF | **4a** | 92 | >95 |
| 2 | **1a** | O | **2b** | $^{i}$Bu | THF | **4b** | 81 | 82 |
| 3 | **1a** | O | **2b** | $^{i}$Bu | THF (PMDTA) | **4b** | 77 | 90 |
| 4 | **1a** | O | **2b** | $^{i}$Bu | $Et_2O$ (PMDTA) | **4b** | 83 | >95 |
| 5 | **1a** | O | **2c** | $^{i}$Pr | THF | **4c** | 91 | 0 |
| 6 | **1a** | O | **2c** | $^{i}$Pr | THF (PMDTA) | **4c** | 95 | 63 |
| 7 | **1a** | O | **2c** | $^{i}$Pr | $Et_2O$ (PMDTA) | **4c** | 89 | 78 |
| 8 | **1a** | O | **2d** | $^{t}$Bu | THF | ***diast*-4d** | 68 | 95 |
| 9 | **1a** | O | **2e** | Ph | THF | **4e** | 78 | 10 |
| 10 | **1a** | O | **2e** | Ph | THF (PMDTA) | **4e** | 82 | 93 |
| 11 | **1a** | O | **2f** | 4-$MeOC_6H_4$ | THF | **4f** | 79 | 0 |
| 12 | **1a** | O | **2f** | 4-$MeOC_6H_4$ | THF (PMDTA) | **4f** | 84 | 53 |
| 13 | **1a** | O | **2f** | 4-$MeOC_6H_4$ | $Et_2O$ (PMDTA) | **4f** | 86 | 73 |
| 14 | **1a** | O | **2g** | 2-Fu | THF | **4g** | 72 | 0 |
| 15 | **1a** | O | **2g** | 2-Fu | THF (PMDTA) | **4g** | 76 | 83 |
| 16 | **1a** | O | **2h** | (*E*)-PhCH=CH | THF | **4h** | 90 | >95 |
| 17 | **1a** | O | **2i** | (*E*)-4-$MeOC_6H_4CH$=CH | THF | **4i** | 89 | 91 |
| 18 | **1a** | O | **2j** | (*E*)-PrCH=CH | THF | **4j** | 73 | >95 |
| 19 | **1a** | O | **2k** | $Me_2CH$=CH | THF | **4k** | 70 | 25 |
| 20 | **1a** | O | **2k** | $Me_2CH$=CH | THF (PMDTA) | **4k** | 73 | 90 |
| 21 | **1a** | O | **2l** | DHP[d] | THF | ***diast*-4l** | 82 | >95 |
| 22 | **1a** | O | **2m** | 1-cyclohexenyl | THF | ***diast*-4m** | 85 | >95 |
| 23 | **1a** | O | **2n** | PhC≡C | THF | **4n** | 86 | >95 |
| 24 | **1a** | O | **2o** | BuC≡C | THF | **4o** | 89 | 63 |
| 25 | **1a** | O | **2o** | BuC≡C | THF (PMDTA) | **4o** | 95 | >95 |
| 26 | **1a** | O | **2p** | TMSC≡C | THF | **4p** | 78 | >95 |
| 27 | **1b** | $CH_2$ | **2a** | Me | THF | **5a** | 91 | >95 |
| 28 | **1b** | $CH_2$ | **2e** | Ph | THF | **5b** | 89 | >95 |
| 29 | **1b** | $CH_2$ | **2h** | (*E*)-PhCH=CH | THF | **5c** | 93 | >95 |
| 30 | **1b** | $CH_2$ | **2n** | PhC≡C | THF | **5d** | 84 | >95 |
| 31 | **1a** | O | **2a** | Me | $Et_2O$ | ***diast*-4a** | 94 | 0 |
| 32 | **1a** | O | **2b** | $^{i}$Bu | $Et_2O$ | ***diast*-4b** | 84 | >95 |
| 33 | **1a** | O | **2c** | $^{i}$Pr | $Et_2O$ | ***diast*-4c** | 88 | >95 |
| 34 | **1a** | O | **2d** | $^{t}$Bu | $Et_2O$ | ***diast*-4d** | 74 | >95 |
| 35 | **1a** | O | **2e** | Ph | $Et_2O$ | ***diast*-4e** | 92 | >95 |
| 36 | **1a** | O | **2f** | 4-$MeOC_6H_4$ | $Et_2O$ | ***diast*-4f** | 89 | >95 |
| 37 | **1a** | O | **2g** | 2-Fu | $Et_2O$ | ***diast*-4g** | 81 | >95 |
| 38 | **1a** | O | **2h** | (*E*)-PhCH=CH | $Et_2O$ | ***diast*-4h** | 84 | 79 |
| 39 | **1a** | O | **2i** | (*E*)-4-$MeOC_6H_4CH$=CH | $Et_2O$ | ***diast*-4i** | 84 | 82 |
| 40 | **1a** | O | **2j** | (*E*)-PrCH=CH | $Et_2O$ | ***diast*-4j** | 80 | >95 |
| 41 | **1a** | O | **2k** | $Me_2CH$=CH | $Et_2O$ | ***diast*-4k** | 90 | >95 |
| 42 | **1a** | O | **2l** | DHP[d] | $Et_2O$ | ***diast*-4l** | 93 | >95 |
| 43 | **1a** | O | **2m** | 1-cyclohexenyl | $Et_2O$ | ***diast*-4m** | 78 | >95 |
| 44 | **1a** | O | **2o** | BuC≡C | $Et_2O$ | ***diast*-4o** | 90 | >95 |
| 45 | **1a** | O | **2p** | TMSC≡C | $Et_2O$ | ***diast*-4p** | 84 | >95 |

[a] All of the reactions in $Et_2O$, THF, or using PMDTA were carried out with lithium enolates **2** generated from silyl enol ethers **6** and BuLi. Reactions in THF were also carried out with lithium enolates **2** generated from methyl ketones **3** and LDA. [b] Isolated yield based on starting carbene **1**. [c] de values were determined by $^1$H NMR on the crude product. [d] DHP = 4,5-dihydro-4*H*-pyran-2-yl.

dimensional (COSY, HMQC, HMBC, and NOESY) NMR spectroscopic analysis. Finally, attempts to accomplish the reaction of carbene complex **1b** with lithium enolates **2** in diethyl ether as solvent were unsuccessful, and the starting carbene complex was recovered after hydrolysis and workup, probably due to a competitive acid−base reaction leading to the abstraction of the $\gamma$-proton of the carbene complex **1b** by the lithium enolate **2**.

In Scheme 2, a tentative mechanism to account for the formation of cyclopentenol derivatives **4**, **5**, and ***diast*-4** is outlined. It is assumed that first a 1,2-addition of the lithium enolates **2** to the carbene complex **1a** occurs to form intermediates **7** or **7′**. A cyclization induced by a 1,2-migration[15] of the pentacarbonyltungsten fragment leads to the bicyclic intermediates **8** or ***diast*-8**. Further elimination of the metal moiety followed by coordination of the metal atom to the carbon−carbon double bond gives intermediates **9** or ***diast*-9**, which, after hydrolysis and metal decoordination, furnishes bicyclic cyclopentenol derivatives **4** or ***diast*-4**, respectively. The opposite diastereoselectivity observed in the formation of **4** or ***diast*-4** when using THF or diethyl ether as solvent can be explained by invoking transition structures with the same geometric disposition as **7** or **7′**. Thus, the formation of **4** when THF or PMDTA was used can be rationalized in terms of coordination of the lithium atom to the THF or the triamine, which lowers the rigidity of the transition structure derived from **7** favoring the approach of the allylic carbon atom of the $\sigma$-allyltungsten moiety to the carbonyl atom. According to this proposal, the

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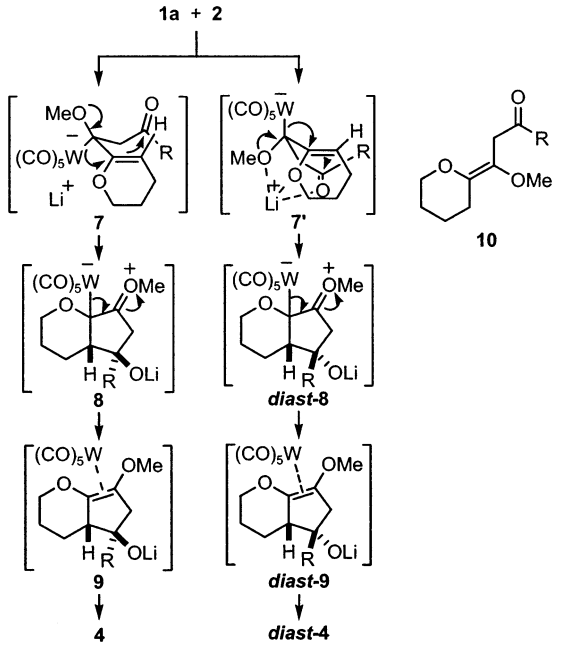
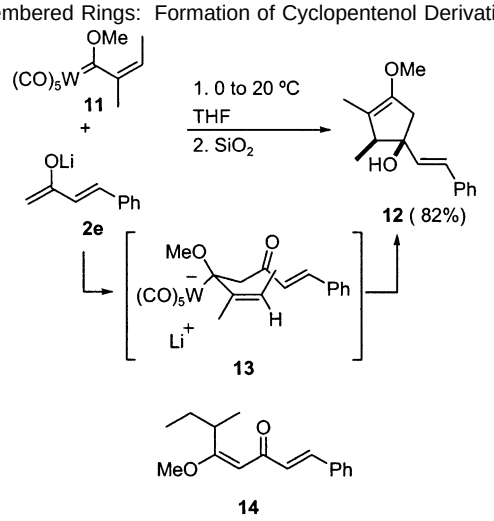
***Scheme 2.*** Proposed Mechanism for the Formation of **4** and ***diast*-4**




bulkier the R groups are, the more disfavored the transition structure derived from **7** is, and so PMDTA, a more strongly coordinating solvent than THF, is required to direct the reaction to **4**. Only bulkier groups such as $^t$Bu, DHP, or 1-cyclohexenyl are positioned on the side of the vinylic hydrogen to avoid interaction with the more sterically demanding methylene group of the dihydropyranyl moiety. In a similar way, the formation of products **5**, derived from the reaction of carbene complex **1b** with lithium enolates **2** in THF, can be explained. Conversely, when the reaction of **1a** with **2** is carried out in diethyl ether, a less coordinating solvent than THF, coordination of the lithium atom to three oxygen atoms favors a transition structure with a geometric disposition of that in **7′**. In this approach, the R group is on the side of the vinylic hydrogen, and the allylic carbon atom of the $\sigma$-allyltungsten moiety is also close to the carbonyl group, therefore leading to the formation of ***diast*-4**, independent of the nature of the substituent R. Support for the above reaction pathways, especially the 1,2-addition, was gained by studying the low-temperature hydrolysis of the reaction mixture, in which probably intermediates **7** or **7′** react at the $\gamma$-position with a proton, giving ketones **10** as single diastereoisomers. The structures of compounds **10** were determined by $^1$H and $^{13}$C NMR experiments, and the configuration of the double bond was determined by NOESY experiments carried out on compound **10d** (R = $^t$Bu). This is the reason lithium enolates generated from silyl enol ethers are preferable to those prepared by deprotonation of methyl ketones with LDA, because the presence of diisopropylamine in the reaction medium in the latter case presumably was responsible for the appearance of ketones **10** when the carbonyl group was less electrophilic.

In our previous paper,[14] $\alpha$-substitution at the carbene complex was invoked to explain the regioselectivity in the reaction of carbene complexes with lithium enolates derived from alkenyl methyl ketones to give five-membered rings instead of seven-membered ones. In the cases described here, both carbene complexes **1a**,**b** are cyclic, and so the reason is not clear. To clarify these facts, carbene complex **11** was prepared and reacted

***Scheme 3.*** Influence of the $\alpha$-Substitution in the Formation of Five-Membered Rings: Formation of Cyclopentenol Derivative **12**

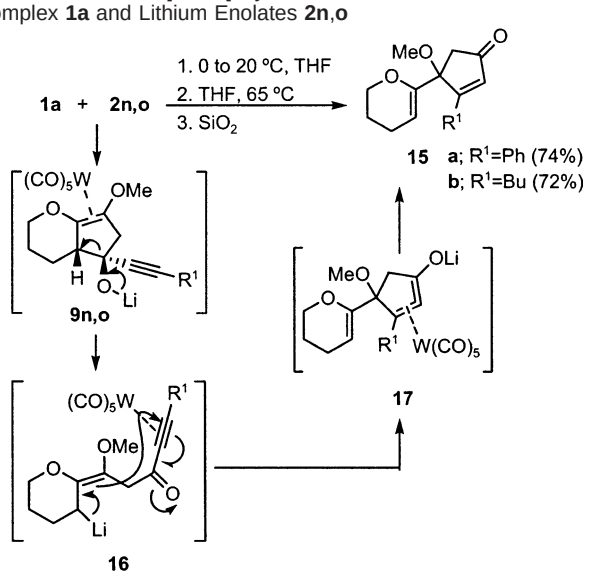



with the lithium enolate of benzylideneacetone **2e**, generated by treatment of silyl enol ether **6e** with BuLi at 0 °C, at temperatures from 0 to 20 °C in THF, affording, after hydrolysis and chromatographic purification, exclusively the five-membered carbocyclic ring **12** in 82% yield and as a single diastereoisomer (Scheme 3). This fact proves that $\alpha$-substitution is responsible for the observed regioselectivity. Intermediate **13**, formed by a nucleophilic attack of the lithium enolate to the carbene carbon atom of carbene complex **11**, is invoked to explain the exclusive formation of **12**. It is interesting to point out that when lithium enolate **2e**, formed by deprotonation of benzylideneacetone **3e** with LDA at 0 °C, is used, ketone **14** is the only product obtained, indicating that the presence of diisopropylamine in the reaction medium promotes protiodemetalation of intermediate **13**. The structures of compounds **12** and **14** were determined by two-dimensional (COSY, HMQC, HMBC, and NOESY) NMR spectroscopic analysis.

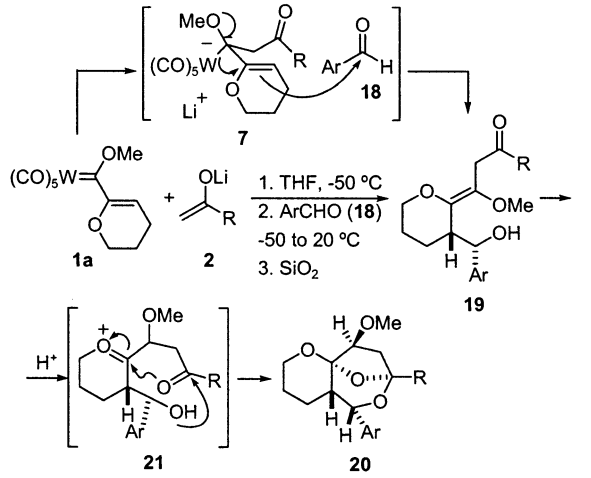
A complementary product to **4** could be formed in the reaction of carbene complex **1a** with alkynyl methyl ketone derived lithium enolates **2n**,**o** if the reaction conditions are slightly changed. Thus, when the reaction mixture was heated under reflux in THF prior to the treatment with silica gel, the formal [4 + 1] cyclization products **15** were isolated in yields higher than 70%.[16] Formation of these products **15** could be rationalized assuming that intermediates **9n**,**o**, generated in the first step of the reaction, could undergo a retro-aldol type reaction affording intermediates **16**. Intramolecular Michael addition of the allyllithium to the ynone moiety in **16**, presumably favored by coordination of a triple bond to the tungsten moiety, would give rise to the cyclopentane derivative **17**, which, after hydrolysis and metal decoordination, would lead to the conjugated cyclopentenones **15** (Scheme 4). The same transformation was not observed starting from lithium enolate **2p**, probably due to the steric hindrance by the TMS group avoiding the Michael addition of the allyllithium to the ynone. On the other hand, the role of the pentacarbonyltungsten fragment appears to be crucial for the outcome of the reaction, because refluxing of

(16) For formal [4 + 1] cyclization reactions with Fischer carbene complexes, see: (a) Fischer, E. O.; Weiss, K.; Burger, K. *Chem. Ber.* **1973**, *106*, 1581−1588. (b) Sierra, M. A.; Söderberg, B.; Lander, P. A.; Hegedus, L. S. *Organometallics* **1993**, *12*, 3769−3771. (c) Barluenga, J.; Aznar, F.; Fernández, M. *Chem.-Eur. J.* **1997**, *3*, 1629−1637. (d) Pfeiffer, J.; Nieger, M.; Dötz, K. H. *Eur. J. Org. Chem.* **1998**, 1011−1022.

***Scheme 4.*** Formal [4 + 1] Cyclization Reaction from Carbene Complex **1a** and Lithium Enolates **2n**,**o**




***Scheme 5.*** Three-Component Coupling Products **19** and **20** from Carbene Complex **1a**, Lithium Enolates **2**, and Aldehydes **18**




the lithium salt of cyclopentenol derivatives **4n**,**o** in THF does not afford, after hydrolysis, the expected cyclopentenones **15**, but only starting material was recovered.

The possibility of trapping intermediates **7** with a proton source to give ketones **10** prompted us to investigate a consecutive one-pot three-component coupling reaction[17] using an aldehyde instead of a proton source. Thus, treatment of carbene complex **1a** with lithium enolates **2** in THF at −50 °C followed by addition of aldehydes **18** at the same temperature, and then warming to 20 °C, led, after hydrolysis with moist silica gel, to the three-component coupling products **19** in moderate to good yields and as single diastereoisomers (Scheme 5 and Table 2). The formation of adducts **19** could be accounted for in a way similar to that proposed for cyclopentenol derivatives **4** with the only difference being that intermediate **7**, generated in the first step, can react intermolecularly with the aldehyde **18**. The relative configuration of the stereocenters

(17) For sequential coupling reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (b) Tietze, L. F.; Haunert, F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Tietze, L. F. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 39. (d) Nicolaou, K. C.; Yue, E. W.; Oshima, T. In *The New Chemistry*; Hall, N., Ed.; Cambridge University Press: Cambridge, 2001; p 168.

***Table 2.*** Three-Component Coupling Reaction of Carbene Complex **1a**, Lithium Enolates **2**, and Aldehydes **18** to Give Hydroxycarbonyl Compounds **19** and or Tricyclic Polyethers **20**

| enolate | R | aldehyde | Ar | product | yield (%)[a] |
|---|---|---|---|---|---|
| **2a** | Me | **18a** | Ph | **19a** | 52 |
| **2e** | Ph | **18a** | Ph | **19b** | 58 |
| **2h** | (*E*)-PhCH=CH | **18a** | Ph | **19c** | 50 |
| **2q** | OEt | **18a** | Ph | **19d** | 59 |
| **2q** | OEt | **18b** | 2-Fu | **19e** | 57[b] |
| **2r** | (−)-8-Ph-menthyl | **18a** | Ph | **19f** | 67[c] |
| **2a** | Me | **18a** | Ph | **20a** | 46 |
| **2d** | $^t$Bu | **18a** | Ph | **20b** | 45 |
| **2d** | $^t$Bu | **18b** | 2-Fu | **20c** | 32 |
| **2e** | Ph | **18a** | Ph | **20d** | 51 |
| **2f** | 4-MeOC$_6$H$_4$ | **18a** | Ph | **20e** | 48 |
| **2f** | 4-MeOC$_6$H$_4$ | **18b** | 2-Fu | **20f** | 38 |
| **2h** | (*E*)-PhCH=CH | **18a** | Ph | **20g** | 45 |
| **2m** | 1-cyclohexenyl | **18a** | Ph | **20h** | 42 |

[a] Isolated yield based on starting carbene **1a**. [b] A 32:1 mixture of diastereoisomers was obtained. [c] A 2:1 mixture of diastereoisomers was obtained.

of **19** formed in the reaction was determined by transformation of these compounds into cyclic derivatives. In fact, these adducts **19** underwent diastereoselective cyclization reactions under mildly acidic conditions at room temperature (just dissolving them in chloroform containing traces of HCl) affording tricyclic compounds **20** (Scheme 5 and Table 2). Protonation of the enol moiety of **19** to give intermediate **21** could promote a domino reaction, which could be initiated by the attack of the alcoholic oxygen to the carbonyl carbon atom followed by the addition of the carbonylic oxygen to the carbon atom to the oxonium ion. The structure and relative configurations of the stereocenters in **20**, and therefore of **19**, were unequivocally determined on the basis of the coupling constants and 2D-NMR experiments carried out on **20a**,**b**. The configuration of the double bond of compounds **19** was assigned by analogy to related compounds **10**. While the bulkiness of the R group of the lithium enolates **2** played an important role in the stereochemical outcome of the intramolecular reaction affording cyclopentenol derivatives **4**, in the intermolecular reaction of intermediate **7** and aldehydes **18**, the formation of the same diastereoisomer of **19** and **20** independent of the nature of the R substituent was observed.

## Conclusions

We have developed an interesting generalization of the 1,2-addition reaction of lithium enolates, derived from simple methyl ketones, to alkenyl carbene complexes, which represents a new strategy for the diastereoselective synthesis of five-membered carbocyclic rings in good yields. The use of more or less coordinating solvents (THF or $Et_2O$) or the presence of PMDTA allows one to synthesize both diastereoisomers with complete or very high diastereoselectivity. Moreover, a mechanism consistent with the experimental data is proposed, in which once again the ability of the recently described 1,2-$(CO)_5$M migration to promote unusual umpolung cyclizations is demonstrated. In this context, the α-substitution in the alkenyl carbene complex appears to be the key to direct the reaction to the five-membered rings, especially when lithium enolates derived from alkenyl methyl ketones are used. In addition, the reaction of alkenyl carbene complexes with alkynyllithium enolates can be conducted to the formal [3 + 2] or [4 + 1] cyclization products with a minor variation in the reaction conditions. One-pot, consecutive, three-component coupling reactions in which an

alkenylcarbene complex, a lithium enolate, and an aldehyde are involved have proved to be an interesting method to diastereoselectively prepare hydroxycarbonyl compounds and tricyclic polyethers. Investigations along these lines as well as on the mechanisms of the reactions and the applications to the organic synthesis are underway in our laboratories.

## Experimental Section

**General.** $^1$H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) or a Bruker DPX-300 (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance as the internal standard ($CHCl_3$, $\delta$ 7.26; $C_6D_6$, $\delta$ 7.16). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; dd, double doublet; ddd, double doublet of doublets; td, triplet of doublets; t, triplet; dt, doublet of triplets; q, quartet; qd, quartet of doublets; qt, quartet of triplets; br, broad; m, multiplet), coupling constants ($J$ in Hz), integration, and assignment. $^{13}$C NMR spectra were recorded on a Bruker AMX-400 (100 MHz) or Bruker DPX-300 (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta$ 76.95; $C_6D_6$, $\delta$ 127.80). Bidimensional NMR experiments (COSY, HMQC, HMBC, and NOESY) were recorded on a Bruker AMX-400 (400 MHz). High-resolution mass spectrometry was carried out on a Finnigan-Mat 95 spectrometer. Melting points were measured on a Büchi-Tottoli apparatus with open capillary tubes and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. All reactions that involved enolates were conducted in flame-dried glassware under an inert atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium metal/benzophenone ketyl. Butyllithium (1.6 M in hexanes) was purchased from Across Organics; methyl ketones **3a**−**h**,**j**,**k**,**m**,**n**,**p**, silyl enol ethers **6a**,**d**,**e**, diisopropilamine, and *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (PMDTA) were purchased from Aldrich and used without previous purification, except PMDTA, which was distilled prior to use. Ketone **3i** was prepared by condensation of acetone and anisaldehyde.[18] Ketones **3l**,**o** were prepared by addition of the corresponding 5,6-dihydro-4*H*-pyran-2-yl or 1-hexynilcuprate derivatives to acetyl bromide or chloride.[19] Silyl enol ethers **6b**,**c**,**f**−**m**,**o**,**p** were prepared in a way similar to the literature procedures. Alkenyl(methoxy)carbene complexes **1a**,**b** and **11** were prepared according to literature procedures.[20]

**General Procedure for the Preparation of Compounds 4, 5, and 12.** In a flame-dried round-bottom flask under nitrogen, enolates **2** were prepared by treatment of ketones **3** (0.44 mmol) with 1 equiv of lithium diisopropilamide at −30 °C for 30 min in 10 mL of THF. Alternatively, enolates **2** were generated by treatment of silyl enol ethers **6** (0.6 mmol) with 1 equiv of BuLi at room temperature for 30 min for silyl enol ethers **6a**,**b**,**d** and at 0 °C for 30 min for the rest of silyl enol ethers **6** in 10 mL of THF or $Et_2O$. If PMDTA was used, enolates **2** were generated exclusively from silyl enol ethers **6** either in THF or in diethyl ether. This cosolvent (3 equiv with respect to BuLi, 1.8 mmol) was added 30 min after BuLi, and the mixture was stirred at 0 °C for 10 min. Carbene complex **1** or **11** (0.4 mmol) was then added at 0 °C, and the mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched with deactivated silica gel and purified by flash column chromatography also in deactivated silica gel (hexanes:ethyl acetate 20:1 to 10:1) to give the compounds **4**, **5**, and **12**.

**(4a*S**,5*R**)-2,3,4,4a,5,6-Hexahydro-7-methoxy-5-methylcyclopenta[*b*]pyran-5-ol (4a).** Silyl enol ether **6a** (92 mg, 0.6 mmol) was treated with BuLi (0.38 mL of 1.6 N solution in hexanes, 0.6 mmol) in THF (10 mL) and carbene complex **1a** (180 mg, 0.4 mmol) to afford compound **4a** (67 mg, 92%) as a colorless oil. $R_f$ 0.33 (hexanes:ethyl acetate, 2:1). $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 3.82 (ddt, $J$ = 10.6, 4.1, 1.8 Hz, 1H; CH*H*O), 3.78 (s, 3H; OMe), 3.21 (ddd, $J$ = 12.5, 10.6, 2.3 Hz, 1H; C*H*O), 2.72 (bs, 1H; OH), 2.66 (dd, $J$ = 14.8, 1.7 Hz, 1H; C*H*HC═), 2.56 (ddt, $J$ = 12.5, 5.0, 1.7 Hz, 1H; CH), 2.33 (dd, $J$ = 14.8, 1.7 Hz, 1H; CH*H*C═), 1.71 (ddtd, $J$ = 12.5, 5.0, 3.6, 1.8 Hz, 1H; C*H*HCH), 1.46 (apparent qt, $J$ = 12.5, 4.1 Hz, 1H; C*H*HCH$_2$O), 1.28−1.21 (m, 1H; CH*H*CH$_2$O), 1.21 (s, 3H; Me), 1.08 (qd, $J$ = 12.5, 3.6 Hz, 1H; CH*H*CH). $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 131.8, 128.1, 74.6, 69.3, 58.5, 50.9, 46.8, 26.2, 25.8, 25.3. HRMS (EI) calcd. for $C_{10}H_{16}O_3$, 184.1099; found, 184.1094. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.29; H, 8.58.

**(1*R**,7a*R**)-2,4,5,6,7,7a-Hexahydro-3-methoxy-1-methyl-1*H*-inden-1-ol (5a).** Silyl enol ether **6a** (92 mg, 0.6 mmol) was treated with BuLi (0.38 mL of 1.6 N solution in hexanes, 0.6 mmol) in THF (10 mL) and carbene complex **1b** (126 mg, 0.4 mmol) to afford compound **5a** (66 mg, 91%) as a colorless oil. $R_f$ 0.40 (hexanes:ethyl acetate, 2:1). $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 3.28 (s, 3H; OMe), 2.85−2.81 (m, 1H; CH*H*C═COMe), 2.47 (dd, $J$ = 15.9, 2.0 Hz, 1H; C*H*HCOH), 2.28 (dd, $J$ = 15.9, 1.7 Hz, 1H; CH*H*COH), 2.16 (apparent ddt, $J$ = 12.5, 4.2, 1.7 Hz, 1H; CH), 1.78−1.57 and 1.17−1.04 (2xm, 6H; C*H*HC*H*$_2$C*H*$_2$C*H*HCH), 1.29 (br s, 1H; OH), 1.12 (s, 3H; Me), 0.84 (qd, $J$ = 12.5, 3.8 Hz, 1H; CH$_2$CH$_2$C*H*HCH$_2$). $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 145.4, 114.8, 76.5, 56.4, 55.9, 46.2, 29.5, 26.7, 26.4, 24.6, 25.1 (Me). HRMS (EI) calcd. for $C_{11}H_{18}O_2$, 182.1307; found, 182.1299. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.61; H, 9.82.

**(1*S**,2*S**)-4-Methoxy-2,3-dimethyl-1-[(*E*)-2-phenylethenyl)]-3-cyclopentenol (12).** Silyl enol ether **6h** (131 mg, 0.6 mmol) was treated with BuLi (0.38 mL of 1.6 N solution in hexanes, 0.6 mmol) in THF (10 mL) and carbene complex **11** (169 mg, 0.4 mmol) to afford compound **12** (80 mg, 82%) as a colorless oil. $R_f$ 0.26 (hexanes:ethyl acetate, 5:1). $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 7.42−7.02 (m, 5H; ArH), 6.95 and 6.34 (2xd, $J$ = 15.9 Hz, 2H; CH═CH), 3.32 (s, 3H; OMe), 2.63−2.44 (m, 3H; $CH_2$ and C*H*Me), 1.74 (s, 3H; ═CMe), 1.59 (s, 1H; OH), 1.05 (d, $J$ = 7.1 Hz, 3H; CH*Me*). $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ = 148.6, 137.5, 135.3, 128.6, 128.5, 126.9, 126.6, 111.8, 78.5, 56.0, 49.3, 44.1, 10.9, 9.7. HRMS (FAB) calcd. for $C_{16}H_{21}O_2$ (M + H)$^+$, 245.1542; found, 245.1547. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.09.

**General Procedure for the Preparation of Compounds *diast*-4.** In a flame-dried round-bottom flask under nitrogen, a solution of silyl enol ethers **6** (0.6 mmol) in diethyl ether (10 mL) was treated with 1 equiv of BuLi at room temperature (**6a**,**b**,**d**) or 0 °C (rest of silyl enol ethers) for 30 min, carbene complex **1a** (0.4 mmol) was added at 0 °C, and the solution mixture was warmed to room temperature and stirred for 30 min. The same workup as for **4** followed.

**(4a*S**,5*S**)-2,3,4,4a,5,6-Hexahydro-7-methoxy-5-(2-methylpropyl)cyclopenta[*b*]pyran-5-ol (*diast*-4b).** Silylenolether **6b** (103 mg, 0.6 mmol) was treated with BuLi (0.38 mL of 1.6 N solution in hexanes, 0.6 mmol) in diethyl ether (10 mL) and carbene complex **1a** (180 mg, 0.4 mmol) to afford compound ***diast*-4b** (76 mg, 84%) as a colorless oil. $R_f$ 0.27 (hexanes:ethyl acetate, 5:1). $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ = 3.91−3.80 (m, 1H; CH*H*O), 3.78 (s, 3H; OMe), 3.26 (td, $J$ = 12.4, 2.6, 1H; C*H*HO), 2.52 (dd, $J$ = 15.4, 1.8 Hz, 1H; CH*H*C═), 2.28 (d, $J$ = 15.4 Hz, 1H; C*H*HC═), 2.27−2.19 (m, 1H; C*H*COH), 1.95−1.82 (m, 1H; C*H*Me$_2$), 1.50−1.12 (m, 7H; OH, C*H*$_2$CHMe$_2$ and C*H*$_2$C*H*$_2$CH$_2$O), 1.03 (d, $J$ = 6.7 Hz, 3H; Me), 0.98 (d, $J$ = 6.7 Hz, 3H; Me). $^{13}$C NMR (75 MHz, $C_6D_6$): $\delta$ = 131.3, 127.7, 75.2, 68.3, 57.6, 48.7, 48.5, 44.6, 24.8, 24.7, 24.6, 24.2, 22.6. HRMS (EI) calcd. for $C_{13}H_{22}O_3$, 226.1569; found, 226.1574. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.14; H, 9.69.

**General Procedure for the Preparation of Cyclopentenones 15.** In a flame-dried round-bottom flask under nitrogen was performed the same reaction used to prepare compounds **4n**,**o**, but, once the mixture

(18) Drake, N. L.; Allen, P., Jr. *Org. Synth., Coll. Vol. 1*; 1948; pp 77−78.
(19) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677−6685.
(20) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9−56.

was at room temperature, it was heated to reflux for 12−20 h. It was then quenched with silica gel, and the residue was purified by flash column chromatography (hexanes:ethyl acetate 20:1).

**4-(5,6-Dihydro-4*H*-pyran-2-yl)-4-methoxy-3-phenyl-2-cyclopentenone (15a).** Ketone **3n** (63 mg, 0.44 mmol) was treated with LDA (0.44 mmol) and carbene complex **1a** (180 mg, 0.4 mmol) in THF (10 mL) to afford, after reflux for 12 h, compound **15a** (80 mg, 74%) as a colorless oil. $R_f$ 0.32 (hexanes:ethyl acetate, 5:1). $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ = 7.81−7.04 (m, 5H; ArH), 6.58 (s, 1H; PhC=C*H*), 6.38 (t, $J$ = 3.7 Hz, 1H; CH=CO), 3.44−3.36 (m, 2H; $CH_2O$), 2.90 (d, $J$ = 18.2 Hz, 1H; C*H*HCO), 2.81 (s, 3H; OMe), 2.65 (d, $J$ = 18.2 Hz, 1H; CH*H*CO), 1.72 (td, $J$ = 6.5, 3.9 Hz, 2H; C=CHC$H_2$), 1.28−1.14 (m, 2H; C$H_2$CH$_2$O). $^{13}$C NMR (75 MHz, $C_6D_6$): $\delta$ = 202.4, 168.6, 153.6, 133.1, 132.1, 130.3, 128.4, 128.1, 95.8, 85.2, 66.2, 49.9, 45.0, 22.2, 19.8. HRMS (EI) calcd. for $C_{17}H_{18}O_3$, 270.1256; found, 270.1259. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.68; H, 6.59.

**General Procedure for the Preparation of Compounds 19.** In a flame-dried round-bottom flask under nitrogen, a solution of enolates **2a**,**e**,**h**,**q**−**s** was prepared by treatment of the corresponding ketones **3** (0.48 mmol) with a solution of lithium diisopropilamide (0.48 mmol) in THF (10 mL) at −30 °C for 30 min. The mixture was cooled to −60 °C, and carbene complex **1a** (0.4 mmol) was added. Once the intense color from the carbene turned much softer (about 5−10 min), aldehydes **18a**,**b** (0.8 mmol) were added, and the mixture was slowly warmed to room temperature. It was then quenched with silica gel and purified by flash column chromatography in hexanes:ethyl acetate (10:1).

**(*E*)-4-{(3*S**)-3-[(*S**)-1-Hydroxy-1-phenylmethyl]-tetrahydropyran-2-ylidene}-4-methoxy-2-butanone (19a).** Acetone (28 mg, 0.48 mmol) was treated with LDA (0.48 mmol) in THF (10 mL), carbene complex **1a** (180 mg, 0.4 mmol), and benzaldehyde (85 mg, 0.80 mmol) to afford compound **19a** (60 mg, 52%) as a colorless oil. $R_f$ 0.43 (hexanes:ethyl acetate, 2:1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.48−7.21 (m, 5H; ArH), 4.99 (d, $J$ = 8.6 Hz, 1H; C*H*Ph), 4.19−4.11 (m, 1H; OC*H*H), 3.52 (ddd, $J$ = 12.0, 9.2, 2.5 Hz, 1H; OCH*H*), 3.18 (s, 2H; C$H_2$COMe), 3.16−3.08 (m, 1H; C*H*CHOH), 2.89 (s, 3H; OMe), 2.40 (br s, 1H; OH), 2.32−1.45 (m, 4H; C$H_2$C$H_2$CH$_2$O), 1.92 (s, 3H; Me). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 206.7, 144.1, 143.3, 137.9, 127.9, 127.4, 126.6, 73.6, 71.1, 56.7, 41.0, 39.7, 28.5, 23.8, 21.5. HRMS (FAB) calcd. for $C_{17}H_{23}O_4$ (M + H)$^+$, 291.1596; found, 291.1601. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.47; H, 7.51.

**General Procedure for the Preparation of Tricyclic Compounds 20.** The same reaction described before for carbene complex **1a** (0.4 mmol), enolates **2a**,**d**,**e**,**f**,**h**,**m** (0.44 mmol), and aldehydes **19a**,**b** (0.8 mmol) was performed. After being quenched with silica gel, solvents were removed, and the residue was filtered in a small amount of silica gel with hexanes:ethyl acetate (20:1) to remove aldehydes **19a**,**b** from the mixture, checking by TLC. After that, ethyl acetate was eluted. Solvents were removed, and the obtained residue was solved in 10 mL of $CHCl_3$ and stirred for 18 h at room temperature. Purification was made by flash column chromatography (hexanes:ethyl acetate, 40:1).

**(1*S**,6*S**,7*S**,9*R**,11*S**)-11-Methoxy-9-methyl-7-phenyl-2,8,12-trioxatricyclo[7.2.1.0$^{1,6}$]dodecane (20a).** Acetone (28 mg, 0.48 mmol) was treated with LDA (0.48 mmol), carbene complex **1a** (180 mg, 0.40 mmol), and benzaldehyde (85 mg, 0.80 mmol) to afford compound **20a** (53 mg, 46%) as a white solid. Mp: 118−120 °C ($CHCl_3$). $R_f$ 0.58 (hexanes:ethyl acetate, 5:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.48−7.26 (m, 5H; ArH), 5.41 (d, $J$ = 4.3 Hz, 1H; C*H*Ph), 3.88−3.74 (m, 3H; $CH_2O$ and C*H*OMe), 3.51 (s, 3H; OMe), 2.49 (dd, $J$ = 14.5, 11.0 Hz, 1H; C*H*HCHOMe), 2.15 (dd, $J$ = 14.5, 4.3 Hz, 1H; CH*H*CHOMe), 2.03 (dt, $J$ = 11.0, 4.3 Hz, 1H; C*H*CHPh), 1.67−1.48 (m, 3H; CH*HCH*$_2$CH$_2$O), 1.61 (s, 3H; Me), 0.98−0.88 (m, 1H; C*H*HCH$_2$CH$_2$O). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 139.3, 128.0, 126.9, 125.8, 105.0, 104.1, 84.5, 73.5, 64.2, 58.4, 40.3, 37.8, 25.0, 24.5, 18.9. HRMS (FAB) calcd. for $C_{17}H_{23}O_4$ (M + H)$^+$, 291.1596; found, 291.1607. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.39; H, 7.60.

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**Supporting Information Available:** Experimental procedures and characterization data for the remaining part of the new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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