Metalated Epoxides as Carbenoids − Further Advances in the Stereospecific Synthesis of Spirocyclopropanes

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The intramolecular cyclopropanation of β,γ-unsaturated metalated epoxides derived from **11** yielded the highly strained tricyclic intermediates **7**. The facile hydrolysis of the latter species afforded the α-keto spirocyclopropanes **8** in a stereospecific fashion. Indeed, the stereochemistry of the starting alkenes **11d–e** governs the relative configuration of the cyclopropanes **8d–e**. Furthermore, these spiro systems readily underwent acid-mediated ring opening by various nucleophiles, leading to the substituted enones **12**.

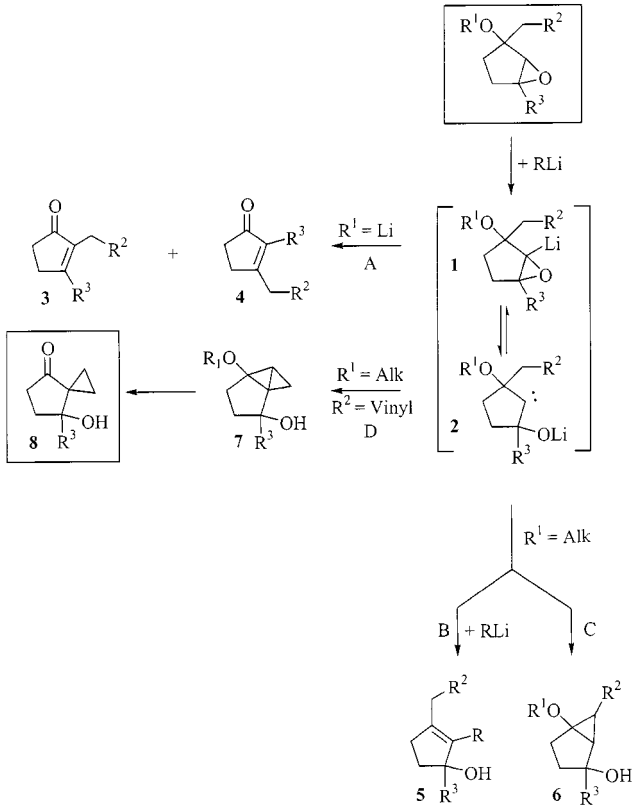
Introduction

Metalated oxiranes are versatile intermediates with wide scope and applicability in synthetic organic chemistry.[1−3] Indeed, depending on the substrate and the reaction conditions, the carbenoid species **1** exhibits various types of reactivity (Scheme 1).[4] We recently surveyed the diverse behavior of epoxide-derived carbenoids.[5] We also demonstrated that, in systems analogous to **1**, the carbene character of the key intermediate **2** depends on the properties of the solvent.[6] In cyclic α-hydroxy epoxide systems, an alkyl 1,2-shift led to the α,β-unsaturated ketones **3** and **4** (pathway A),[7] whereas the insertion of an organolithium reagent, followed by alkoxide elimination, was predominant in cyclic α-alkoxy epoxides (pathway B).[8] The latter route produced allylic alcohols **5** in very good yield. However, in some instances we observed the formation of cyclopropanes **6**, which arose from the insertion of the carbenoid into an adjacent C−H bond (pathway C).[9] Finally, the last example illustrated in Scheme 1 is an intramolecular [2 + 1] cycloaddition, which afforded the highly strained tricyclic intermediate **7** (pathway D).[10] This reaction occurred when R^1 = alkyl and R^2 = vinyl. The facile hydrolysis of **7** under mildly acidic conditions provided a novel route to the spirocyclopropanes **8**.

The purpose of this article is to report full experimental details on the carbenoid-mediated synthesis of spirocyclopropanes **8**. Also, we describe the transformation of these molecules into enones by nucleophilic ring opening of the cyclopropyl moiety.

Results and Discussion

The starting β,γ-unsaturated epoxides **11**, which serve as direct precursors to the tricyclic systems **7**, were prepared by reacting various vinyl Grignard reagents with the substituted cyclopentenone oxides **9**. This afforded the *syn* α-hydroxy epoxides **10** in nearly quantitative yield. The *syn* selectivity of this process has already been observed and commented on by others.[11] Protection of the hydroxyl group of **10** (NaH/MeI) furnished the epoxides **11a−e** in overall yields ranging from 71 to 91% (Scheme 2).



Scheme 1

Our initial experiments on these cyclopropanation reactions were conducted on the β,γ-unsaturated epoxide **11a** with *n*BuLi as base in Et_2O (10^{-1} M concentration, room temperature) and led to the exclusive formation of the allylic alcohol (presumably by a mechanism analogous to

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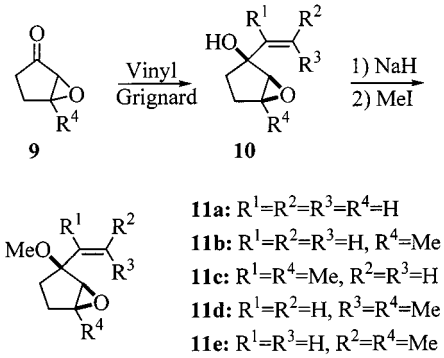
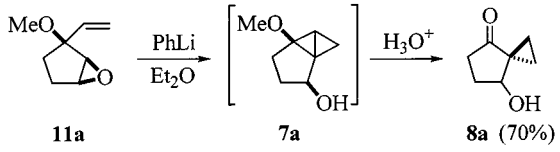


Scheme 2

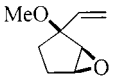
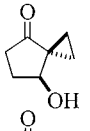
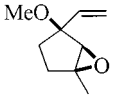
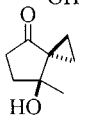
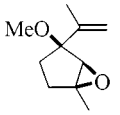
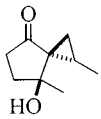
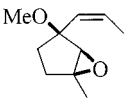
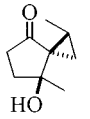
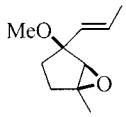
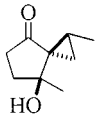
pathway B in Scheme 1). To enhance the intramolecular cyclopropanation, we used highly dilute solutions of the epoxide (10^{-3} M concentration, room temperature). This afforded the desired spirocyclopropane **8a**, albeit in poor yield (<15%). To avoid the competing intermolecular insertion reaction, phenyllithium emerged as the reagent of choice (10^{-1} M concentration, room temperature): Under the above conditions, spirocyclopropane **8a**[12] was obtained in 70% yield (Scheme 3).



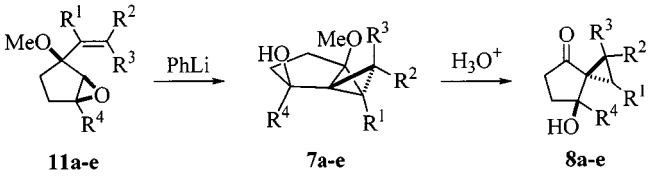
Scheme 3

To gauge the scope and limitations of the phenyllithium-mediated cyclopropanation, we attempted the reaction on a number of *cis*- and *trans*-disubstituted alkene epoxides **11a**−**e**. Table 1 summarizes the results obtained for the synthesis of spirocyclopropanes **8a**−**e**.

Table 1. Examples of spirocyclopropanation

entry	substrate (**11**)	product (**8**)	yield
a			70
b			88
c			71
d			83
e			75

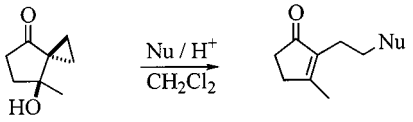
In every case, the overall yield was satisfactory. The relative configuration of the cyclopropyl stereocenters in **8c**−**e** was established by NOE measurements. On the basis of these assignments, we concluded that the entire process — comprising a [2 + 1] cycloaddition and a ring opening — is stereospecific. The latter step proceeds by an S_E2-type mechanism. The relative configuration of the newly created stereocenters in **8d**−**e** was therefore governed by the *Z* or *E* stereochemistry of the parent double bond. The stereospecificity of the two-step process can be rationalized as illustrated in Scheme 4.



Scheme 4

Although the isolation of the transient tricyclic heptane **7** was not feasible for mono-substituted alkenes, we were able to isolate this intermediate by chromatography in the case of the β-disubstituted substrate **11c**. Thus, the phenyllithium-induced cyclopropanation of **11c** ($R^1 = R^4 = Me$ and $R^2 = R^3 = H$) led to the highly strained compound **7c** in 74% yield. Upon treatment with $THF/H_2O/SiO_2$, **7c** was converted smoothly to the ketocyclopropane **8c**.

The final objective of this study was to design a new route to enone systems through nucleophilic ring opening of cyclopropanes such as **8b** (Scheme 5). Indeed, the combination of an α-hydroxy spirocyclopropane and an adjacent carbonyl group should facilitate the acid-mediated addition of various nucleophiles to the cyclopropane ring. To corroborate this hypothesis, substrate **8b** was treated with the following reagent combinations: aqueous *para*-toluenesulfonic acid, concentrated HCl, or *para*-toluenesulfonic acid in methanol. These reactions furnished adducts **12a**−**c**, in which the introduction of the nucleophile proceeded with concomitant dehydration of the cyclopentanone.



H_2O / pTsOH: **12a** (95%), Nu: OH
HCl: **12b** (95%), Nu: Cl
MeOH/ pTsOH: **12c** (81%), Nu: OCH_3

Scheme 5

In conclusion, we have shown that the intramolecular carbenoid-mediated cyclopropanation of β,γ-unsaturated epoxides afforded, in a two-step process, spirocyclopropanes in a stereospecific fashion. These systems could readily be converted into the corresponding enones by a tandem ring opening/dehydration process.

Experimental Section

General Methods: ^1H and ^{13}C spectra were recorded at 250 and 62.9 MHz unless otherwise stated. Chemical shifts are reported in ppm from TMS ($\delta = 0$). All reactions were performed under argon. Flash column chromatography was performed on Merck silica gel (230−400 mesh). THF was distilled from sodium/benzophenone. Reagents were purchased from Aldrich Chemical Co.

General Procedure for the Synthesis of α-Methoxy Epoxides 11a−e. Synthesis of 2-Methoxy-2-vinyl-6-oxabicyclo[3.1.0]hexane (11a): Vinylmagnesium bromide (1.1 mL of a 1 M soln/THF, 1.1 equiv.) was added dropwise at 0 °C to a solution of cyclopentenone oxide (0.1 g, 1 mmol, 1 equiv.) in 10 mL of THF. This mixture was stirred for 30 min. at 0 °C, quenched with a 10% NH_4Cl solution and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was taken up in 5 mL of THF and NaH (0.04 g of a 60% suspension in oil, 1.2 equiv.) was added portionwise. After 5 min., methyl iodide (0.1 mL, 1.6 equiv.) was added dropwise. The mixture was stirred at room temperature for 3 hours. The reaction was then quenched with H_2O and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica (EtOAc/pentane, 5:95) to yield pure 2-methoxy-2-vinyl-6-oxa-bicyclo[3.1.0]hexane (**11a**; oil, 0.105 g, 75%). ^1H NMR ($CDCl_3$): δ = 1.56 (m, 4 H), 3.27 (s, 3 H), 3.35 (s, 1 H), 3.43 (d, J = 2.7 Hz, 1 H), 5.23 (m, 2 H), 5.76 (dd, J = 11.1 and 17.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.5, 28.3, 52.5, 55.3, 58.1, 76.5, 116.3, 138.1. − HRMS calcd. for $C_8H_{12}O_2$ 140.0837; found 140.0842.

4-Methoxy-1-methyl-4-vinyl-6-oxabicyclo[3.1.0]hexane (11b): Oil (0.240 g, 85%). ^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H), 1.55 (m, 3 H), 1.85 (m, 1 H), 3.18 (s, 1 H), 3.20 (s, 3 H), 5.07 (d, J = 17.8 Hz, 1 H), 5.16 (d, J = 10.3 Hz, 1 H), 5.73 (dd, J = 10.3 and 17.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.8, 29.6, 30.1, 52.3, 62.6, 63.7, 84.9, 115.7, 138.6. − IR (neat): $\tilde{\nu}$ = 1305, 1418, 1455, 1640, 2938 cm^{-1}. − MS (CI/NH_3): m/z (%) = 172 (100) [M + 18].

4-Isopropenyl-4-methoxy-1-methyl-6-oxabicyclo[3.1.0]hexane (11c): Oil (0.132 g, 91%). ^1H NMR ($CDCl_3$): δ = 1.40 (s, 3 H), 1.52 (m, 3 H), 1.70 (d, J = 0.8 Hz, 3 H), 1.85 (m, 1 H), 3.18 (s, 3 H), 3.26 (s, 1 H), 4.72 (d, J = 2.7 Hz, 1 H), 4.96 (dd, J = 0.8 and 2.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.8, 18.3, 29.7, 30.7, 52.5, 63.4, 76.4, 86.8, 113.0, 145.3. − MS (CI/NH_3): m/z (%) = 186 (100) [M + 18].

(*Z*)-4-Methoxy-1-methyl-4-propenyl-6-oxabicyclo[3.1.0]hexane (11d): Oil (0.094 g, 78%). ^1H NMR ($CDCl_3$): δ = 1.36 (s, 3 H), 1.58 (m, 3 H), 1.77 (dd, J = 1.3 and 7.2 Hz, 3 H), 1.90 (m, 1 H), 3.19 (s, 3 H), 3.34 (s, 1 H), 5.13 (dd, J = 1.3 and 11.4 Hz, 1 H), 5.69 (qd, J = 7.2 and 11.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 14.5, 17.9, 29.9, 32.3, 51.8, 64.8, 65.3, 85.3, 128.5, 131.1. − IR (neat): $\tilde{\nu}$ = 1307, 1424, 1451, 1649, 2945 cm^{-1}. − MS (CI/NH_3): m/z (%) = 186 (100) [M + 18].

(*E*)-4-Methoxy-1-methyl-4-propenyl-6-oxabicyclo[3.1.0]hexane (11e): Oil (0.120 g, 71%). ^1H NMR ($CDCl_3$): δ = 1.37 (s, 3 H), 1.52 (m, 3 H), 1.67 (d, J = 6.2 Hz, 3 H), 1.88 (m, 1 H), 3.10 (s, 1 H), 3.22 (s, 3 H), 5.37 (d, J = 14.6 Hz, 1 H), 5.55 (qd, J = 6.2 and 14.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.9, 18.3, 29.8, 30.4, 52.2, 62.7, 64.5, 84.5, 127.0, 131.6. − MS (CI/NH_3): m/z (%) = 186 (100) [M + 18].

General Procedure for the Synthesis of Spirocyclopropanes 8a−e. Synthesis of 7-Hydroxyspiro[2.4]heptan-4-one (8a): Phenyllithium (0.33 mL of a 1.8 M solution in cyclohexane/Et_2O, 2 equiv.) was added over a period of 10 min. at room temperature to a solution of 2-methoxy-2-vinyl-6-oxabicyclo[3.1.0]hexane (**11a**; 0.042 g, 0.3 mmol, 1 equiv.) in 30 mL of Et_2O. The mixture was stirred for 30 min. at room temp. The reaction was then quenched with H_2O and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica (EtOAc/pentane, 3:7) to yield pure 7-hydroxy-spiro[2.4]heptan-4-one (**8a**)[13] as an oil (0.026 g, 70%). ^1H NMR ($CDCl_3$): δ = 0.98 (m, 1 H), 1.15 (m, 3 H), 2.06 (m, 1 H), 2.25 (m, 2 H), 2.58 (m, 1 H), 4.10 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 12.5, 18.6, 30.6, 35.9, 36.8, 75.0, 217.5. − MS (CI/NH_3): m/z (%) = 144 (100) [M + 18], 161 (64) [M + 35].

7-Hydroxy-7-methyl-spiro[2.4]heptan-4-one (8b): Oil (0.184 g, 88%). − ^1H NMR ($CDCl_3$): δ = 0.91 (m, 4 H), 1.12 (s, 3 H), 1.59 (s, 1 H), 1.98 (m, 1 H), 2.22 (m, 2 H), 2.53 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 12.5, 17.0, 24.9, 36.0, 36.8, 39.8, 76.4, 218.1. − IR (neat): $\tilde{\nu}$ = 1716 (CO), 3396 (OH). − HRMS calcd. for $C_8H_{12}O_2$ 140.0837; found 140.0839.

7-Hydroxy-1,7-dimethyl-spiro[2.4]heptan-4-one (8c) Oil (0.062 g, 71%). − ^1H NMR ($CDCl_3$): δ = 0.95 (s, 1 H), 0.98 (s, 1 H), 1.23 (d, J = 6.4 Hz, 3 H), 1.40 (s, 3 H), 1.66 (s, 1 H), 1.69 (m, 1 H), 1.95 (m, 1 H), 2.12 (m, 1 H), 1.33 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 13.5, 22.1, 23.0, 25.5, 36.3, 39.1, 43.2, 76.7, 216.2. − IR (neat): $\tilde{\nu}$ = 1713 (CO), 3446 (OH) cm^{-1}. − MS (CI/NH_3): m/z (%) = 137 (29) [M − OH], 154 (100) [M^+], 172 (61) [M + 18]. − HRMS calcd. for $C_9H_{14}O_2$ 154.0993; found 154.0998.

7-Hydroxy-1,7-dimethyl-spiro[2.4]heptan-4-one (8d): Oil (0.035 g, 75%). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.94 (dd, J = 3.6 and 7.2 Hz, 1 H), 1.18 (dd, J = 3.6 and 9.2 Hz, 1 H), 1.25 (s, 1 H), 1.33 (d, J = 6.5 Hz, 3 H), 1.38 (s, 3 H), 1.68 (m, 1 H), 1.97 (m, 1 H), 2.19 (m, 1 H), 2.32 (dd, J = 8.4 and 18.1 Hz, 1 H), 2.66 (ddd, J = 8.4, 12.4 and 18.1 Hz, 1 H). − ^{13}C NMR (MeOD): δ = 13.5, 23.6, 25.3, 28.0, 35.8, 38.4, 42.8, 78.8, 218.1. − IR (neat): $\tilde{\nu}$ = 1714 (CO), 3446 (OH) cm^{-1}. − MS (CI/NH_3): m/z (%) = 154 (20) [M^+], 172 (35) [M + 18], 189 (100) [M + 35]. − HRMS calcd. for $C_9H_{14}O_2$ 154.0993; found 154.0996.

7-Hydroxy-1,7-dimethyl-spiro[2.4]heptan-4-one (8e): Oil (0.029 g, 83%). − ^1H NMR ([D_6]acetone): δ = 0.77 (dd, J = 3.7 and 7.3 Hz, 1 H), 1.00 (dd, J = 3.8 and 7.3 Hz, 1 H), 1.08 (s, 3 H), 1.15 (d, J = 6.1 Hz, 3 H), 1.62 (m, 1 H), 2.16 (m, 2 H), 2.35 (m, 1 H), 2.63 (m, 1 H). − ^{13}C NMR (MeOD): δ = 11.5, 22.4, 22.6, 25.5, 37.3, 37.4, 43.7, 76.7, 216.2. − IR (neat): $\tilde{\nu}$ = 1724 (CO), 3409 (OH) cm^{-1}. − MS (CI/NH_3): m/z (%) = 154 (100) [M^+], 172 (56) [M + 18]. − HRMS calcd. for $C_9H_{14}O_2$ 154.0993; found 154.0998.

5-Methoxy-2,6-dimethyl-tricyclo[4.1.0.0.1.5]heptan-2-ol (7c): Oil (0.022 g, 70%). − ^1H NMR ($CDCl_3$): δ = 1.13 (s, 3 H), 1.18 (s, 3 H), 1.33 (m, 1 H), 1.51 (s, 1 H), 1.88 (d, J = 2.0 Hz, 1 H), 1.94 (d, J = 2.0 Hz, 1 H), 1.95 (m, 2 H), 2.23 (m, 1 H), 3.16 (s, 3 H). − ^{13}C NMR (CD_2Cl_2): δ = 10.0, 24.4, 25.4, 27.0, 34.0, 42.3, 42.7, 56.7, 78.4, 99.7. − IR (neat): $\tilde{\nu}$ = 3410 (OH) cm^{-1}. − HRMS calcd. for $C_9H_{13}O_2$ [M − CH_3] 153.0915; found 153.0961.

General Procedure for the Synthesis of Cyclopentenones 12a−c. Synthesis of 2-(2-Hydroxyethyl)-3-methylcyclopent-2-enone (12a): *p*-TsOH (0.1 g, 1.5 equiv.) and 1 mL of H_2O were added at room temperature to a solution of spirocyclopropane **8b** (0.05 g, 0.36 mmol, 1 equiv.) in dichloromethane (3 mL). The mixture was stirred for 24 hours at room temperature. The reaction mixture was then diluted with H_2O and extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated solution of

$NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residual solid was chromatographed on silica (Et_2O/pentane, 3:7) to yield pure 2-(2-hydroxyethyl)-3-methylcyclopent-2-enone (**12a**)[14] as an oil (0.048 g, 95%). ^1H NMR ($CDCl_3$): δ = 2.02 (s, 3 H), 2.43 (m, 6 H), 2.79 (br. s, 1 H), 3.61 (t, J = 5.8 Hz, 2 H). − ^{13}C NMR: ($CDCl_3$) δ = 17.3, 27.3, 32.0, 34.2, 61.4, 139.0, 172.2, 212.1. − MS (CI/NH_3): m/z (%) = 141 (100) [M + 1], 158 (93) [M + 18].

2-(2-Chloroethyl)-3-methylcyclopent-2-enone (12b): Oil (0.033 g, 95%). Prepared as described for **12a** using 1 mL of 12 N HCl instead of H_2O (without *p*-TsOH). ^1H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.35 (m, 2 H), 2.53 (m, 2 H), 2.63 (t, J = 6.7 Hz, 2 H), 3.59 (t, J = 6.7 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.6, 26.8, 31.9, 34.2, 42.9, 136.5, 173.4, 209.1. − HRMS calcd. for $C_8H_{11}ClO$ 158.0498; found 158.0501.

2-(2-Methoxyethyl)-3-methylcyclopent-2-enone (12c):[14] Oil (0.029 g, 81%). Prepared as described for **12a** using 1 mL of MeOH instead of H_2O. ^1H NMR ($CDCl_3$): δ = 2.01 (s, 3 H), 2.28 (m, 2 H), 2.31 (t, J = 6.8 Hz, 2 H), 2.43 (m, 2 H), 3.24 (s, 3 H), 3.34 (t, J = 6.8 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.4, 23.8, 31.7, 34.3, 58.5, 70.6, 137.2, 172.3, 209.5.

Acknowledgments

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[1] J. K. Crandall, M. Apparu, *Org. React.* **1983**, 345−443.
[2] T. Satoh, *Chem. Rev.* **1996**, *96*, 3303−3325.
[3] E. Doris, L. Dechoux, C. Mioskowski, *Tetrahedron Lett.* **1994**, *35*, 7943−7946.
[4] It has recently been reported that simple metalated epoxides can be trapped by electrophiles, see D. M. Hodgson, S. L. M. Norsikian, *Org. Lett.* **2001**, *3*, 461−463.
[5] E. Doris, L. Dechoux, C. Mioskowski, *Synlett* **1998**, 337−343.
[6] E. Doris, C. Mioskowski, L. Dechoux, C. Agami, *J. Org. Chem.* **1998**, *63*, 3808−3809.
[7] E. Doris, L. Dechoux, C. Mioskowski, *J. Am. Chem. Soc.* **1995**, *117*, 12700−12704.
[8] L. Dechoux, E. Doris, C. Mioskowski, *Chem. Commun.* **1996**, 549−550.
[9] L. Dechoux, C. Agami, E. Doris, C. Mioskowski, *J. Org. Chem.* **1999**, *64*, 9279−9281.
[10] C. Agami, L. Dechoux, E. Doris, C. Mioskowski, *Tetrahedron Lett.* **1997**, *38*, 4071−4074.
[11] J. Sepúlveda, C. Soriano, J. Roquet-Jalmar, R. Mestres, J. Riego, *Bull. Chem. Soc. Fr.* **1987**, 189−192.
[12] M. C. Pirrung, P. M. Kenney, *J. Org. Chem.* **1987**, *52*, 2335−2336.
[13] W. Adam, I. Erden, *J. Org. Chem.* **1978**, *43*, 2737−2738.
[14] H. Stetter, H. T. Leinen, *Chem. Ber.* **1983**, *116*, 254−263.

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