Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6709–6711

Formation of 1-methylene-2-vinylcyclopropane by intramolecular S'_E-cycloalkylation reaction

Sven Brandau, Roland Fröhlich and Dieter Hoppe*

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany

Received 23 June 2005; revised 25 July 2005; accepted 26 July 2005
Available online 10 August 2005

Abstract—The synthesis of a substituted (*Z*)-2-(2-methylenecyclopropyl)vinyl *N*,*N*-dialkylcarbamate is presented. Via α-deprotonation of a 4-chloromethyl-2,4-dienyl carbamate and succeeding intramolecular S'_E-cycloalkylation reaction, the diastereomerically pure cyclopropane is formed.

Methylenecyclopropanes and some of their derivatives have been known for several years in organic synthesis, but there are only few methods reported for the synthesis of functionalized 1-methylene-2-vinylcyclopropanes.[1] Elimination reactions of halo- and dihalocyclopropanes offer an access to this class of compounds but 1-methylene-2-alk-1-enylcyclopropanes are obtained as a mixture of the corresponding cis- and trans-isomers.[1c,2]

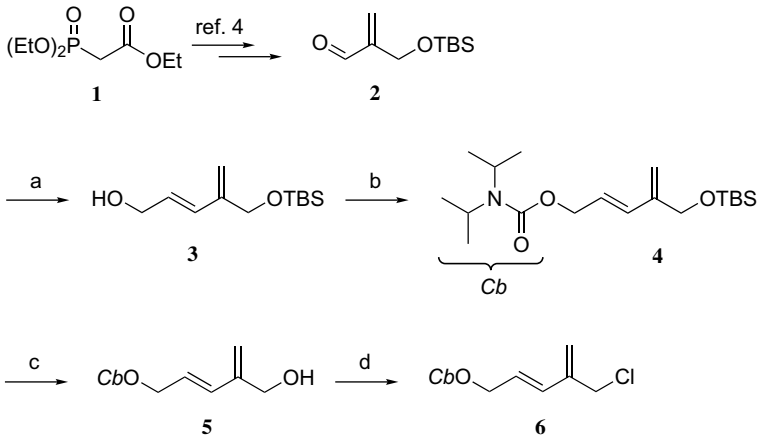
The exact mechanism of these base-induced eliminations and double-bond migrations, which leads to 1-methylene-2-vinylcyclopropanes, is not yet completely understood. Here, we report a simple method for the formation of a substituted diastereomerically pure (*Z*)-configured 2-(2-methylenecyclopropyl)vinyl ester derivative based on α-deprotonation of the ω-functionalized dienyl carbamate **6**.[3] **6** was synthesized in few steps starting from the aldehyde **2** which was prepared according to the literature from phosphonate **1** (Scheme 1).[4] After a Horner–Wadsworth–Emmons chain elongation of the aldehyde **2** with triethyl phosphonoacetate, the ethyl ester was isolated as a crude product. Due to the instability of the ester, direct reduction with DIBAL-H was necessary. The corresponding allylic alcohol **3** was obtained after two steps in 24% yield. Treatment of the alcohol **3** with sodium hydride and *N*,*N*-diisopropylcarbamoyl chloride furnished the carbamate **4** in 59% yield. Removal of the TBS group with TBAF yielded the carbamate **5** in 90%. Transformation of the hydroxy group of **5** into chloro via an Appel reaction leads to the (2*E*)-dienyl carbamate **6** in 80% yield as a single diastereomer.

After deprotonation of the carbamate **6** with *n*-butyllithium in the presence of different bis-tertiary diamines at −78 °C in diethyl ether, the diastereomerically pure (*Z*)-configured cyclopropane **8** could be isolated. Using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), ***rac*-8** was obtained in 33% yield as a crystalline solid (Fig. 1).[7] With (−)-sparteine (+)-**8** was obtained in 52% yield with an enantiomeric excess of 50%.[8,9] Due to the fast epimerization of the intermediate, configurationally unstable dienyllithium intermediate **7**, we obtained only a moderate enantiomeric excess. The (*Z*):(*E*) ratio of the product was >98:2 in all cyclization reactions.

The *N*,*N*-diisopropylcarbamoyl group is required for activation and the regioselective deprotonation of the dienyl moiety. It acidifies the dienylic protons at C-1 and fixes the lithium counter ion after the deprotonation of **6** in the α-position.[5] In the cyclization reactions, at least 2 equiv of *n*-butyllithium were required. This can be explained by the high acidity of the formed vinylic proton at the C-1 position in the cyclopropane **8**. Quantitative removal of one α-dienylic proton in **8** is therefore just possible when using at least 2 equiv of *n*-butyllithium. The α-lithiated intermediate **7** reacts from the (2*E*)-*endo*-conformation *endo*-**7** to form by an intramolecular S'_E-cycloalkylation the (*Z*)-configured 2-(2-methylenecyclopropyl)vinyl ester **8** (Scheme 2).[6]

Keywords: Cyclopropanes; Cycloalkylation; Carbamates.
* Corresponding author. Fax: +49 (0) 251 8336531; e-mail: dhoppe@uni-muenster.de

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.138



Scheme 1. Reagents and conditions. (a) (i) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, Et_2O; (ii) DIBAL-H, toluene, −78 °C, 24%; (b) *Cb*Cl, NaH, THF, 59%; (c) TBAF, Et_2O, 90%; (d) PPh_3, Cl_3CCN, C_6H_5Cl, 80 °C, 80%.

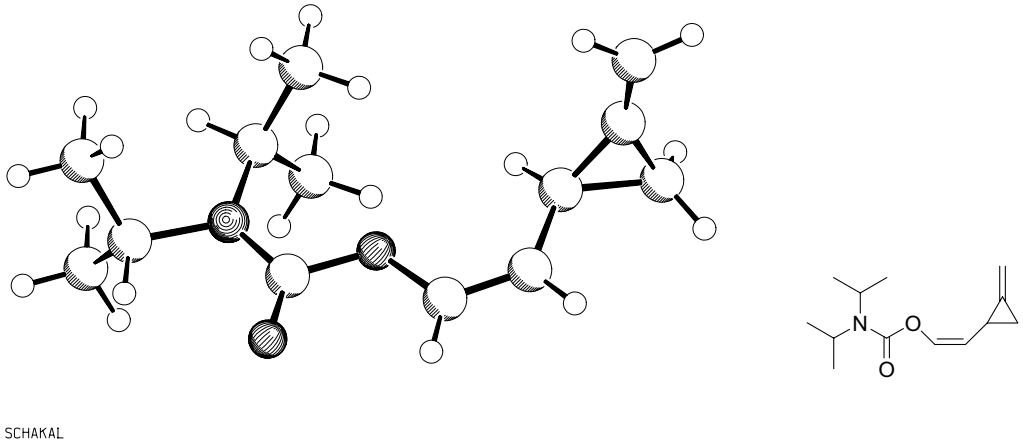
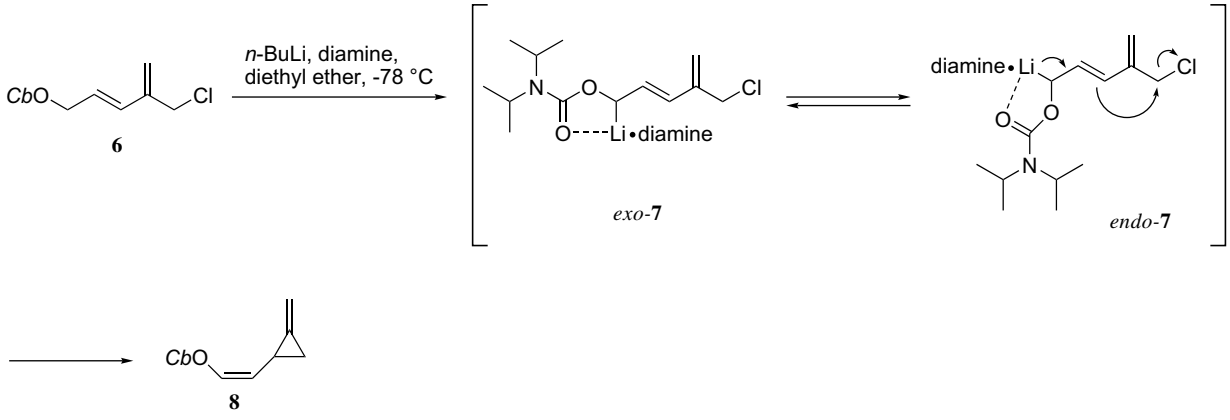


Figure 1. Solid-state structure of (*Z*)-*N*,*N*-diisopropylcarbamic acid [2-(2-methylenecycloprop-1-yl)vinyl] ester (**8**).



Scheme 2. Synthesis of 2-(2-methylenecycloprop-1-yl)vinyl ester **8**.

In conclusion, we have shown a simple way for the synthesis of the highly strained (*Z*)-configured 2-(2-methylenecyclopropyl)vinyl ester **8** in good yield, high diastereoselectivity, and moderate enantioselectivity.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 424) and the Fonds der Chemischen Industrie.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.138.

References and notes

1. (a) Shields, T. C.; Billups, W. E.; Lepley, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 4749–4751; (b) Arora, A.; Binger, P. *Synthesis* **1974**, 801–803; (c) Brouwer, A. M.; Jacobs, H. J. C. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 48–53; (d) de Meijere, A.; Kozhushkov, S. I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* **2001**, 3607–3614; (e) Binger, P.; Brinkmann, A.; Wedemann, P. *Synthesis* **2002**, *10*, 1344–1346.
2. Billups, W. E.; Shields, T. C.; Chow, W. Y.; Deno, N. C. *J. Org. Chem.* **1972**, *37*, 3676–3678.
3. Review: (a) Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376–2410; . *Angew. Chem., Int. Ed.* **1997**, *36*, 2282–2316; (b) Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R.; Hoppe, D. *Angew. Chem.* **2004**, *116*, 1447–1451; . *Angew. Chem., Int. Ed.* **2004**, *43*, 1423–1427; Reviews: (c) Hoppe, D.; Marr, F.; Brüggemann, M. In *Organolithiums in Enantioselective Synthesis, Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin, 2003; Vol. 5, pp 61–138; (d) Christoph, G.; Hoppe, D. Asymmetric Deprotonation with Alkyllithium/(−)-Sparteine. In *The Chemistry of Organolithium Compounds. Part II*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004, pp 1058–1164.
4. (a) Mantlo, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 8129–8133; (b) Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501–1513.
5. (a) Krämer, T.; Schwark, J.-R.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 7037–7040; (b) Hoppe, D.; Zschage, O. *Angew. Chem.* **1989**, *101*, 67–69; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69–71; (c) Hoppe, D.; Zschage, O. *Tetrahedron* **1992**, *48*, 5657–5666; (d) Krämer, T.; Hoppe, D. *Tetrahedron Lett.* **1987**, *28*, 5149–5152.
6. (a) Bosshardt, H.; Schlosser, M. *Helv. Chim. Acta* **1980**, *23*, 2393–2403; (b) Schlosser, M. *Angew. Chem.* **1974**, *86*, 751–788; *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701–706.
7. X-ray crystal structure analysis: formula $C_{13}H_{21}NO_2$, $M = 223.31$, colourless crystal $0.20 \times 0.20 \times 0.10$ mm, $a = 9.126(1)$, $b = 8.049(1)$, $c = 18.654(1)$ Å, $\beta = 103.20(1)°$, $V = 1334.0(2)$ Å^3, $\rho_{calc} = 1.112$ g cm^{-3}, $\mu = 5.89$ cm^{-1}, empirical absorption correction ($0.891 \leqslant T \leqslant 0.944$), $Z = 4$, monoclinic, space group $P2_1/n$ (No. 14), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 9437 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 2191 independent ($R_{int} = 0.051$) and 1696 observed reflections [$I \geqslant 2\sigma(I)$], 150 refined parameters, $R = 0.047$, $wR^2 = 0.136$, max. residual electron density 0.14 (−0.18) e Å^{-3}, hydrogens calculated and refined as riding atoms. Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN (Otwinowski, Z., Minor, W. *Methods in Enzymology*, **1997**, *276*, 307–326), absorption correction Denzo (Otwinowski, Z., Borek, D., Majewski, W., Minor, W. *Acta Cryst.* **2003**, *A59*, 228–234), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics SCHAKAL (Keller, E., 1997).Crystallographic data (excluding structure factors) for the structure of **8** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 260661. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
8. The enantiomeric excess could be determined by lithiation of (+)-**8** at the vinylic C-1 position with TMEDA and *n*-butyllithium at −78 °C in diethyl ether, trapping the lithium species with (*R*)-phenylethyl isocyanate, and determination of the dr in the crude ^{1}H NMR spectra. The absolute configuration of **8** remains unclear.
9. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2-methylenecyclopropyl-1-yl)vinyl] ester **8**. Representative experimental procedure for **8**: The diamine (0.35 mmol) was dissolved under argon atmosphere in diethyl ether (2 mL), and the solution was cooled to −78 °C. *n*-Butyllithium (0.22 mL, 0.35 mmol, 1.6 M in *n*-hexane) was added and the reaction mixture was stirred for 15 min. After the addition of **6** (45 mg, 0.17 mmol) the reaction mixture was stirred for an additional 3 h. The reaction mixture was quenched at −78 °C with ethanol (0.5 mL) and water (0.5 mL) and was allowed to warm up to room temperature. The mixture was diluted with diethyl ether (30 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography (diethyl ether/*n*-pentane = 1:10) to give **8** as colourless liquid, which crystallizes on storage at 0 °C. Data for **8**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.08$ (m, 1H), 1.27 (bd, 12H), 1.58 (ddt, 1H, $J = 9.1$ Hz, $J = 2.0$ Hz, $J = 0.6$ Hz), 3.98 (br d, 2H), 4.31 (dd, 1H, $J = 9.5$ Hz, $J = 6.6$ Hz); 5.42 (m, 1H), 5.48 (m, 1H), 7.06 (dd, 1H, $J = 6.6$ Hz, $J = 0.9$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 11.5$, 13.0, 20.4, 21.5, 45.7, 46.8, 104.0, 112.2, 135.3, 135.6, 155.7; GC-TOF: $m/z = 223$, 164, 128, 101, 95, 86, 79 (100), 78, 77, 52, 50; IR (film) 3102, 3073, 2996, 2970, 2875, 1707, 1667, 1472, 1438, 1371, 1310, 1288, 1234, 1213, 1187, 1143, 1066, 1047, 906, 890, 762 [cm^{-1}]; Exact mass (EI) calcd for $C_{13}H_{21}NO_2$ 246.1465, found 246.1440. $[\alpha]_D^{20}$ +1.1 (*c* 0.29, $CHCl_3$) at 50% ee (er = 75:25).