Tetrahedron Letters 49 (2008) 6959–6961

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly stereoselective allylic ethylation with alkoxytitanacyclopropane reagents. Synthesis of (1*R*/*S*,7*R*)-1,7-dimethylnonyl propanoate, the Western corn rootworm sex attractant

Vladimir E. Isakov, Oleg G. Kulinkovich *

Department of Organic Chemistry, Belarusian State University, Nezavisimosti Av. 4, Minsk 220030, Belarus

ARTICLE INFO

Article history:
Received 9 July 2008
Revised 11 August 2008
Accepted 19 August 2008
Available online 23 August 2008

Keywords:
Alkoxytitanacyclopropane reagents
Allylic ethers
Allylic ethylation
Diastereoselectivity
Pheromones

ABSTRACT

Allylic ethylation of 2-((*E*)-dodec-2-en-4-yloxy)tetrahydro-2*H*-pyran with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide proceeds via a S_N2' pathway to afford (*E*)-3-methyltridec-4-ene with excellent *syn*-diastereoselecivity. This transformation is used as a key step in the synthesis of (1*R*/*S*,7*R*)-1,7-dimethylnonyl propanoate, the Western corn rootworm (*Diabrotica virgifera virgifera*) sex attractant.

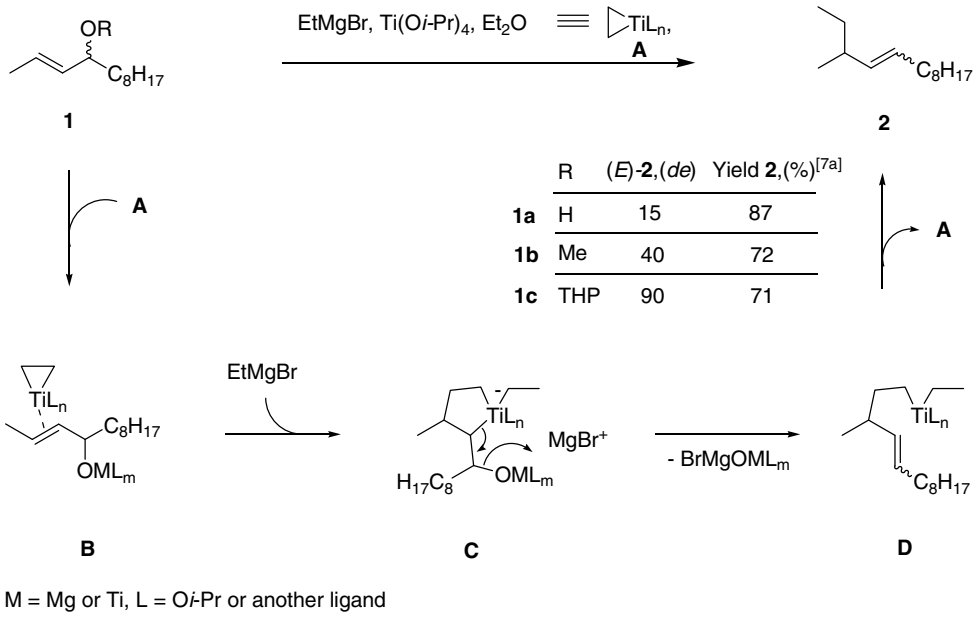
The development of efficient methods for the preparation of chiral allylic alcohols[1] and their derivatives[2] increases the synthetic importance of stereoselective carbon–carbon bond forming reactions. Highly *anti*-S_N2' stereoselective alkylations of allylic esters have been observed in copper-catalyzed[2k–o] and heteroatom-assisted noncatalyzed reactions of organomagnesium compounds.[3] In contrast, the use of *o*-diphenylphosphanylbenzoate as a reagent-directing leaving group permits reactions of the corresponding allylic esters with organomagnesium compounds in a highly *syn*-S_N2' stereoselective fashion.[2p–s] Herein, we disclose the ability of a tetrahydropyranyloxy group to play the same directing role toward alkoxytitanacyclopropane reagents. As an application of this method of regio- and diastereoselective ethylation of THP-protected allylic alcohols, we have synthesized (1*R*/*S*,7*R*)-1,7-dimethylnonyl propanoate **3**, the Western corn rootworm sex attractant.[4]

Recently, we reported that interaction of racemic allylic alcohols and their ethers with alkoxytitanacyclopropane reagents, generated in situ by treatment of titanium(IV) alkoxides[5,6] with ethylmagnesium bromide, afforded the products of S_N2' substitution of hydroxy or alkoxy groups with an ethyl group.[7] For example, allylic alcohol **1a** and its derivatives **1b,c** were converted under these conditions into methyl-branched alkenes **2**. The suggested mechanism of the reaction includes coordination of the substrate **1** with alkoxytitanacyclopropane species **A**, followed by transformation of the resulting complex **B** to titanacyclopentane ate-complex **C**, intramolecular 1,2-elimination of a metal oxide fragment, and disproportionation of dialkyltitanium intermediate **D** (Scheme 1).[7a] Among the compounds **1a–c**, only tetrahydropyranyl derivative **1c** gave alkene **2** with high trans-diastereoselectivity.

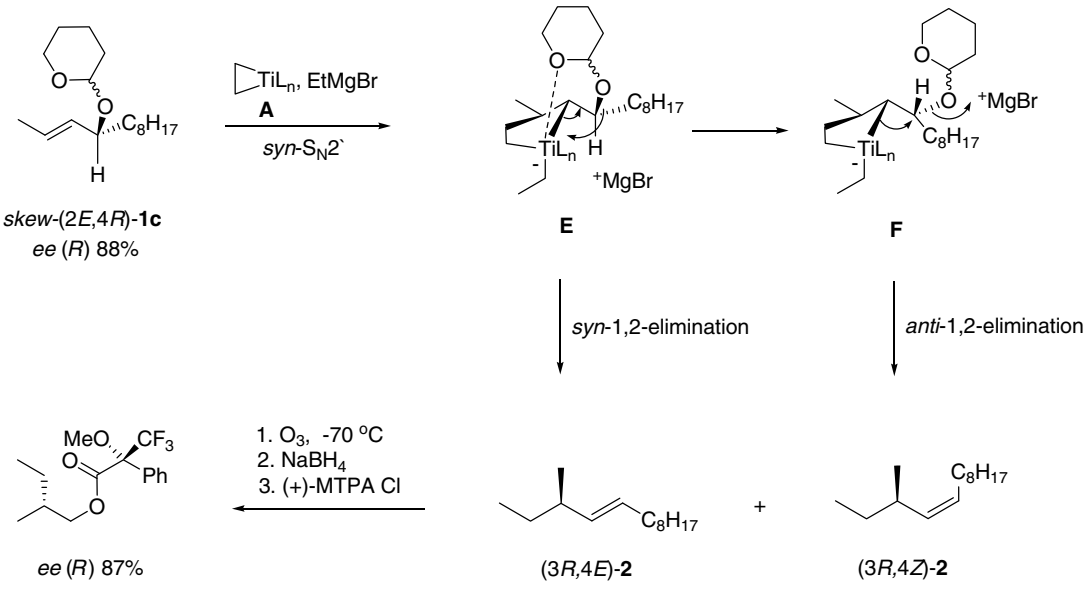
Herein, we report the trans-diastereoselectivity of the allylic ethylation of tetrahydropyranyl derivative **1c** combined with high 1,3-asymmetric induction during the formation of a stereogenic center in a *syn*-S_N2' stereoselective fashion. Thus, treatment of a 0.4 M solution of allylic alcohol (2*E*,4*R*)-**1a** (ee 88%)[8] and titanium(IV) isopropoxide in ether with a 1.2 M solution of ethylmagnesium bromide gave alkene (3*R*,4*E*)-**2** with a de of 15% and an ee of 14%, whereas its THP analogue (2*E*,4*R*)-**1c** (a mixture of diastereomers) afforded the same product with much better stereoselectivity (de 90%, ee 69%). The concentration of the reagent solutions influenced the stereoselective formation of the stereogenic center significantly. Thus, the use of fourfold diluted solutions of tetrahydropyranyl derivative **1c**, titanium(IV) isopropoxide, and ethylmagnesium bromide led to the formation of alkene (3*R*,4*E*)-**2** with de 90% and ee 87%,[9] corresponding to 99% *syn*-S_N2' chirality transfer (Scheme 2). The enantiomeric purity and absolute configuration of the mixture of alkenes **2** obtained were ascertained by ozonolysis, followed by reduction with sodium borohydride and analysis of the ^{1}H NMR spectrum of the (+)-MTPA ester of the resulting 2-methylbutanol (Scheme 2).[10,11]

* Corresponding author. Tel.: +375 17 2095459; fax: +375 17 2265609.
E-mail address: kulinkovich@bsu.by (O. G. Kulinkovich).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.08.063



Scheme 1.

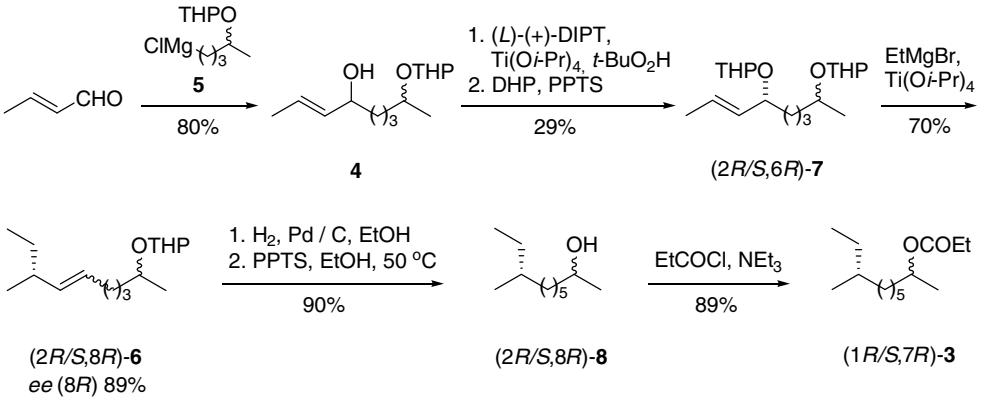


Scheme 2.

The conversion of allylic alcohol derivative (2*E*,4*R*)-**1c** to the alkenes **2** with (*R*) configuration at the stereogenic center at C-3 corresponds to addition of alkoxytitanacyclopropane reagent **A** to the disubstituted double bond in *syn*-fashion with respect to the leaving THPO-group in a *skew*-conformation[12] of the substrate. Such a stereochemical pathway of the reaction suggests the formation of putative tricyclic complex **E**, where the octyl substituent occupies the less hindered *exo*-position (Scheme 2). It should be mentioned that the allylic ethylation of compound **1c** proceeded with higher *syn*-S_N2' stereoselectivity than trans-stereoselectivity (99% and 90%, correspondingly), evidencing the ability for formation of (3*R*,4*Z*)-olefin **2** via an *anti*-1,2-elimination of the metal oxide fragment in titanacyclopentane intermediate **F**.

As mentioned above, the ready availability of chiral allylic alcohols[1] makes the allylic ethylation of their THP derivatives with alkoxytitanacyclopropane reagents **A** a potentially useful tool for synthetic applications. In this work, we employed this transformation in the synthesis of propanoate (1*R*/*S*,7*R*)-**3**, the pheromone of the Western corn rootworm (*Diabrotica virgifera virgifera*). The attractive activity of this compound in field testing was comparable with the activity of the natural pheromone[4] (1*R*,7*R*)-**3** (Scheme 3).

rac-Alcohol **4** was prepared by the reaction of crotonic aldehyde with 4-(tetrahydro-2*H*-pyranyl-2-oxy)pentylmagnesium chloride (**5**). After resolution of *rac*-**4** by stoichiometric Sharpless asymmetric epoxidation,[13] alcohol (2*R*/*S*,6*R*)-**4** was obtained with ee 90% (Scheme 3).[14] Protection of the hydroxyl group in the latter and treatment of resulting THP-ether **7** with an excess of ethylmagnesium bromide in the presence of 1 equiv of titanium(IV) isopropoxide led to olefin (2*R*/*S*,8*R*)-**6** (de 90%, ee 89%) in 70% yield.[15] Palladium-catalyzed hydrogenation of the double bond in (2*R*/*S*,8*R*)-**6**,[16] followed by deprotection and esterification of alcohol (2*R*/*S*,8*R*)-**8**[17] led to the target propanoate (1*R*/*S*,7*R*)-**3**.[4,18]



Scheme 3.

In conclusion, we have reported a highly stereoselective *syn*-S_N2' allylic ethylation reaction of the THP-derivatives **1c** and **7** with alkoxytitanacyclopropane reagents and the use of this transformation in the key step of the synthesis of (1*R*/*S*,7*R*)-1,7-dimethylnonyl propanoate, the Western corn rootworm sex attractant.

References and notes

1. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103–158; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (c) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (d) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978; (e) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (f) Corey, E. J.; Helal, C. J. *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
2. For Cu-mediated reactions, see: (a) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984; (b) Arai, M.; Lipshutz, B. H.; Nakamura, E. *Tetrahedron* **1992**, *48*, 5709; (c) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895; (d) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923; (e) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem.* **2004**, *116*, 2480; *Angew. Chem., Int. Ed.* **2004**, *43*, 2426; (f) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585; (g) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529; (h) Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 7375; (i) Alexakis, A.; Tomassini, A.; Andrey, O.; Bernardinelli, G. *Eur. J. Org. Chem.* **2005**, 1332; (k) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *35*, 1517; Calaza, M. I.; Hupe, E.; Knochel, P. Org. Lett. **2003**, *5*, 1059; (l) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111; (m) Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409; (n) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem.* **2005**, *117*, 4703; *Angew. Chem., Int. Ed.* **2005**, *44*, 4627; (o) Soorukram, D.; Knochel, P. *Angew. Chem.* **2006**, *118*, 3768; *Angew. Chem., Int. Ed.* **2006**, *45*, 3686; (p) Breit, B.; Demel, P.; Studte, C. *Angew. Chem.* **2004**, *116*, 3874; *Angew. Chem., Int. Ed.* **2004**, *43*, 3786; (q) Breit, B.; Herber, C. *Angew. Chem.* **2004**, *116*, 3878; *Angew. Chem., Int. Ed.* **2004**, *43*, 3790. For Zr-mediated reactions, see: (r) Morken, J. P.; Hoveyda, A. H. *Angew. Chem.* **1996**, *108*, 1378; *Angew. Chem., Int. Ed.* **1996**, *35*, 1263; (s) Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485. For other metal-mediated reactions, see:(t) Felkin, H.; Joly-Goudket, M. *Tetrahedron Lett.* **1981**, *22*, 1157; (u) Hayashi, T.; Konishi, M.; Yokota, K.; Kumada, M. *J. Organomet. Chem.* **1985**, *285*, 359; (v) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273; (w) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621; (x) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Eur. J. Org. Chem.* **2006**, 5995.
3. (a) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205; (b) Adams, J. A.; Heron, N. M.; Koss, A.-M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854.
4. (a) Guss, P. L.; Tumlinson, J. H.; Sonnet, P. E.; Proveaux, A. T. *J. Chem. Ecol.* **1982**, *8*, 545; (b) Guss, P. L.; Sonnet, P. E.; Carney, R. L.; Branson, T. F.; Tumlinson, J. H. *J. Chem. Ecol.* **1984**, *10*, 1123; (c) Mori, K.; Watanabe, H. *Tetrahedron* **1984**, *40*, 299; (d) Dobson, I. D.; Teal, P. E. A. *J. Chem. Ecol.* **1987**, *13*, 1331.
5. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244; *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027; (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Savchenko, A. I.; Prityts kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294; *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 250; (c) Kulinkovich, O. G.; Vasilevskii, D. A.; Savchenko, A. I.; Sviridov, S. V. *Zh. Org. Khim.* **1991**, *27*, 1428; *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 1249; (d) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.
6. For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (b) Kulinkovich, O. G. *Izv. AN Ser. Chim.* **2004**, 1022; *Russ. Chem. Bull., Int. Ed.* **2004**, 1065.
7. (a) Kulinkovich, O. G.; Epstein, O. L.; Isakov, V. E.; Khmel'nitskaya, E. A. *Synlett* **2001**; (b) Kulinkovich, O. G. *Pure Appl. Chem.* **2000**, *72*, 1715; (c) Matyushenkov, E. A.; Churikov, D. G.; Sokolov, N. A.; Kulinkovich, O. G. *Zh. Org. Khim.* **2003**, *39*, 514.
8. Alcohol (2*E*,4*R*)-**1a** has been prepared in 34% yield by the resolution of all-*rac* alcohol **1a** using the catalytic Sharpless asymmetric epoxidation: Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922; Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
9. *Experimental procedure:* To a solution of 0.8 g (3 mmol) THP-ether **1c** and 0.9 ml (3 mmol) of Ti(O*i*-Pr)$_4$ in 35 ml of Et_2O, 45 ml of an ethereal solution of EtMgBr (12 mmol) was added dropwise for over 0.5 h at room temperature, and the mixture was stirred for an additional 30 min. After acidic work-up (15 ml of 10% aq H_2SO_4) and extraction with ether (3 × 10 ml), the combined organic layers were washed with saturated $NaHCO_3$ and NaCl, dried over $MgSO_4$, and the solvent was evaporated. (*E*)-3-Methyl-4-tridecene (**2**) (containing 5% of the (*Z*)-isomer by GC–MS-analysis) (0.42 g, 71%) was isolated by column chromatography over silica gel (eluent—hexane). Spectroscopic data of compound **2** were in accordance with those already published.[11]
10. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
11. Mori, K.; Takikawa, H. *Liebigs Ann. Chem.* **1991**, 497.
12. Cha, G. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.
13. Martin, V. S.; Woodard, S. S.; Katzuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
14. For the determination of the stereochemical purity of alcohol (2*R*/*S*,6*R*)-**4**, its (+)-MTPA-derivative[13] was analyzed by ^{1}H NMR spectroscopy after the removal of the THP-protective group.
15. *Experimental procedure:* To a solution of 0.2 g (0.613 mmol) of THP-ether (2*R*/*S*,6*R*)-**7** and 0.18 ml (0.613 mmol) of Ti(O*i*-Pr)$_4$ in 15 ml of Et_2O, 25 ml of an ethereal solution of EtMgBr (4.3 mmol) was added dropwise for over 0.5 h at room temperature, and the mixture was stirred for an additional 30 min. After treatment with saturated NH_4Cl and extraction with ether (3 × 5 ml), the combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and the solvent was evaporated. THP-ether (*E*)-(2*R*/*S*,8*R*)-**6** (containing 5% of the (*Z*)-isomer by GC–MS-analysis) (0.11 g, 70%) was isolated by column chromatography over silica gel (eluent—hexane/ether). Compound (*E*)-**6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.4 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 1.8H), 1.20 (d, *J* = 6.4 Hz, 1.2H), 1.16–1.62 (m, 10H), 1.61–1.87 (m, 2H), 1.89–2.06 (m, 3H), 3.42–3.52 (m, 1H), 3.66–3.82 (m, 1H), 3.84–3.96 (m, 1H), 4.59–4.64 (m, 0.4H), 4.67–4.72 (m, 0.6H), 5.23 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.28–5.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.72, 19.06, 19.69, 20.08, 20.38, 20.40, 21.52, 25.46, 25.50, 25.56, 25.90, 29.81, 31.19 (two carbon atoms), 32.58, 35.84, 35.85, 36.94, 38.32, 38.34, 62.36, 62.80, 70.95, 70.97, 73.70, 73.72, 95.53, 98.55, 128.23, 128.36, 136.35, 136.49; IR (CCl_4) 2856, 1455, 1375, 1260, 1077 cm^{-1}.
16. (a) Kallmerten, J.; Balestra, M. *J. Org. Chem.* **1986**, *51*, 2855; (b) Azerad, R.; Buisson, C. *Tetrahedron* **1988**, *44*, 6407; (c) Lamers, Y. M. A. W.; Rusu, G.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **2003**, *59*, 9361.
17. Spectroscopic data of compounds **3** and **8** were in accordance with those already published.[18b–d]
18. (a) Sonnet, P. E.; Camey, R. L.; Henrick, C. *J. Chem. Ecol.* **1985**, *11*, 1371; (b) Ferreira, J. T. B.; Simonelli, F. *Tetrahedron* **1990**, *46*, 6311; (c) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Org. Chem.* **1992**, *57*, 3631; (d) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789; (e) Chow, S.; Kitching, W. *Chem. Commun.* **2001**, 1040; (f) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779.