JOC Article
pubs.acs.org/joc

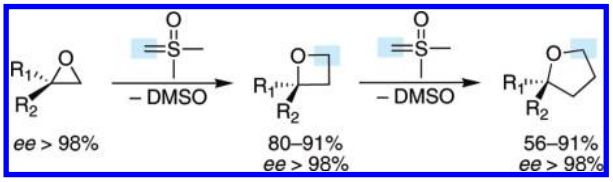
Stereospecific Consecutive Epoxide Ring Expansion with Dimethylsulfoxonium Methylide

Ekaterina D. Butova,[§,‡] Anastasiya V. Barabash,[§] Anna A. Petrova,[§] Christian M. Kleiner,[‡] Peter R. Schreiner,*[,‡] and Andrey A. Fokin*[,§,‡]

[§]*Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy 37, 03056 Kiev, Ukraine, and* [‡]*Institut für Organische Chemie, Justus-Liebig University, Heinrich-Buff-Ring 58, D-35392 Giessen, Germany*

prs@org.chemie.uni-giessen.de; aaf@xtf.ntu-kpi.kiev.ua

Received July 6, 2010



Consecutive ring-expansion reactions of oxiranes with dimethylsulfxonium methylide were studied experimentally and modeled computationally at the density functional theory (DFT) and second-order Møller−Plesset (MP2) levels of theory utilizing a polarizable continuum model (PCM) to account for solvent effects. While the epoxide to oxetane ring expansion requires 13−17 kcal mol^{-1} activation and occurs at elevated temperatures, the barriers for the ring expansions to oxolanes are higher (ca. 25 kcal mol^{-1}) and require heating to 125 °C. Further expansions of these oxolanes to the six-membered oxanes are hampered by high barriers (ca. 40 kcal mol^{-1}). We observe the complete conservation of the enantiomeric purities for the nucleophilic ring expansions of enantiomeric 2-mono- and 2,2-disubstituted epoxides and oxetanes with dimethylsulfoxonium methylide. This is a convenient general approach for the high-yielding preparation of optically active four- and five-membered cyclic ethers from oxiranes.

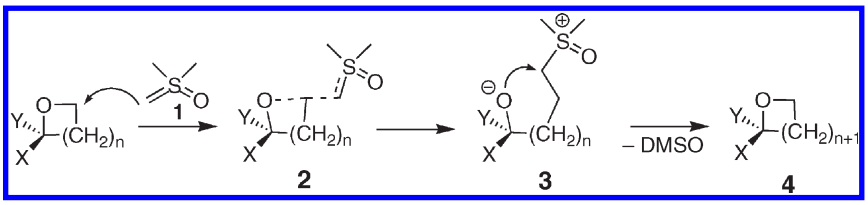
Introduction

Small four- and five-membered cyclic ethers (oxetanes and oxolanes) are the key structural fragments of many biologically active compounds. For instance, the oxetane ring is present in taxol[1,2] and its analogue baccatin,[3] laureatin,[4] oxetin,[5] and oxetanocin.[6] The incorporation of an oxetane ring into the structure of *N*,*N*-dimethyl-4-(*p*-*tert*-butylphenyl)-butylamine results in remarkable changes of its physicochemical characteristics such as lipophilicity, amphiphilicity, hERG liability, and basicity of the nearby amine group.[7] Optically active oxetanes are important intermediates in the preparation of biologically active compounds, such as sarracenin,[8] erogorgiaene,[9,10] and some others.[11] Chiral oxetanes are also intermediates in organic synthesis: the enantioselective oxetane ring openings promoted by Lewis acids[12] or peroxides[13] give, respectively, hydroxyketones and 3-hydroperoxyalkanols, whereas with Brønsted acids optically active alkenes, unsaturated

(1) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. *J. Org. Chem.* **1991**, *56*, 5114–5119.
(2) Heiberg, H.; Johansson, L.; Gropen, O.; Ryan, O. B.; Swang, O.; Tilset, M. *J. Am. Chem. Soc.* **2000**, *122*, 10831–10845.
(3) Samaranayake, G.; Neidigh, K. A.; Kingston, D. G. *J. Nat. Prod.* **1993**, *56*, 884–898.
(4) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109–1112.
(5) Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A.; Matsumoto, T. *J. Antibiot.* **1984**, *37*, 1324–1332.
(6) Saksena, A. K.; Ganguly, A. K.; Girijavallabhan, V. M.; Pike, R. E.; Chen, Y.-T.; Puar, M. S. *Tetrahedron Lett.* **1992**, *33*, 7721–7724.
(7) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739.
(8) Hoye, T. R.; Richardson, W. S. *J. Org. Chem.* **1989**, *54*, 688–693.
(9) Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290–1296.
(10) Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841–2843.
(11) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420–12421.
(12) Bach, T.; Eilers, F. *J. Org. Chem.* **1999**, *64*, 8041–8044.
(13) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591–4593.
(14) Marchand, A. P.; Wang, Y.; Ren, C.-t.; Vidyasagar, V.; Wang, D. *Tetrahedron* **1996**, *52*, 6063–6072.

DOI: 10.1021/jo101330p Published on Web 08/18/2010

SCHEME 1. Consecutive Oxacycle Ring Expansion with Dimethylsulfoxonium Methylide (1)



alcohols, or diols form.[14,15] The stereoselective reductive opening of oxetanes with lithium powder in the presence of catalytic amounts of DTBB followed by treatment with various electrophiles leads to optically active alcohols.[16] The oxolane ring is a fragment of many enantiomerically pure marine polycyclic esters,[17] alkaloids,[18−22] lignanes,[23] and terpenoids.[24]

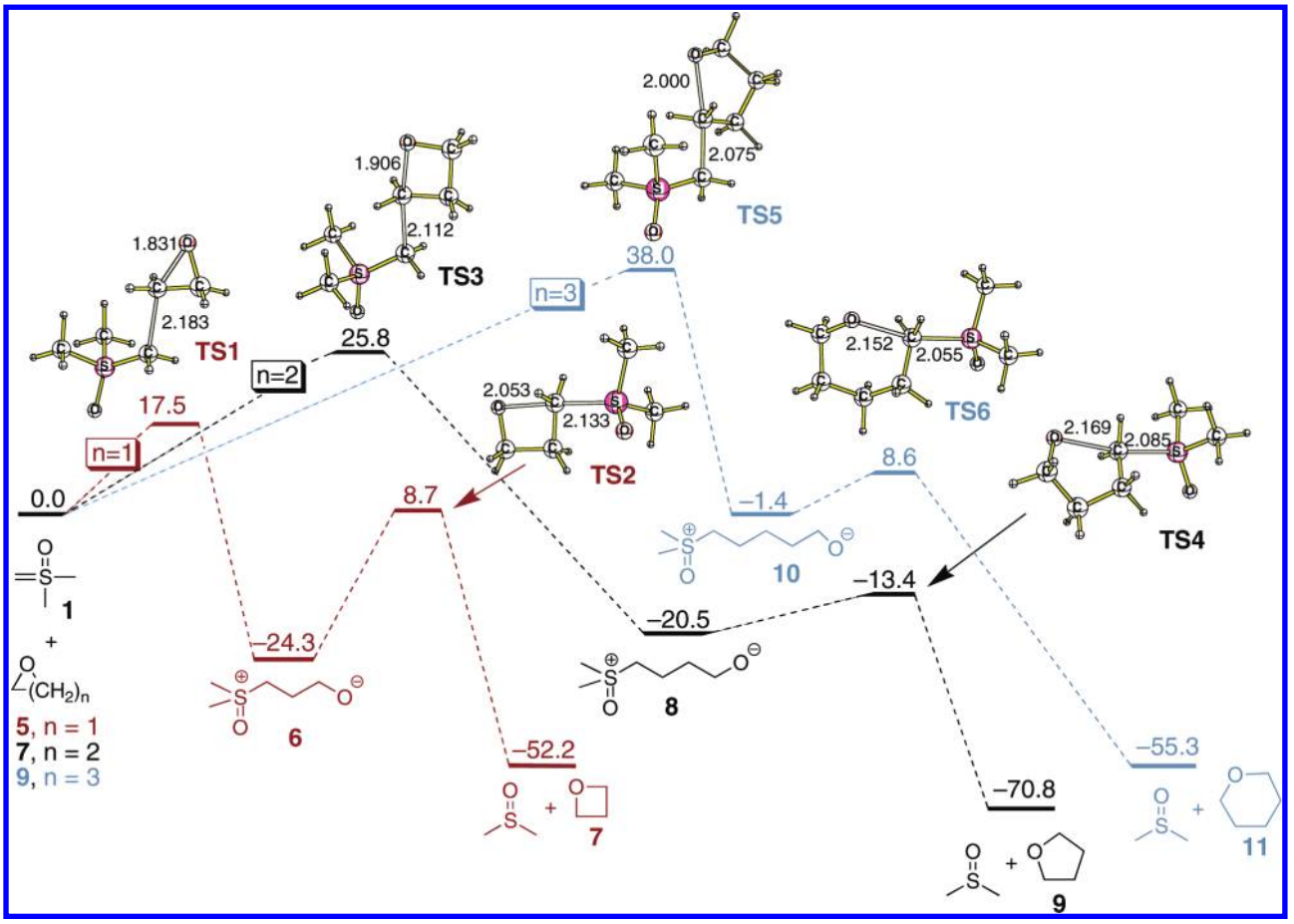
The existing procedures for the preparation of optically active oxetanes and oxolanes utilizing diols,[13,14] oxiranes,[11] ketones,[25] acetaldehyde and cyclopentadiene,[8] tosylates,[10] etc.[26] either require many steps[14,27] or expensive reagents or give products with low enantiomeric excess.[25] It is well documented that the methylenation of epoxides with dimethylsulfoxonium methylide (**1**) produces oxetanes in good yields under mild reaction conditions.[28]

Therefore it is somewhat surprising that the methylenation of optically active epoxides with **1** has not received more attention, since they are readily available in high ee via Sharpless[29,30] or Shi[14,31−34] as well as many other[35−38] epoxidations or through a large variety of other methods.[39−49] Only recently optically active 2-(3-chlorophenyl)oxetane was obtained via ring expansion of 3-chlorostyreneoxide.[50] For the preparation of optically active 2,2-disubstituted oxetanes the one-pot consecutive methylenation of prochiral ketones in the presence of an optically active heterobimetallic complex was suggested.[51] The reaction involves the formation[52] of optically active oxiranes; the enantiopurity was slightly amplified in the second step as a result of partial kinetic resolution of the intermediates. This transformation is applicable to the preparation of optically pure (ee > 99%) methyl oxetanes in good preparative yields (62−88%). However, the results are quite sensitive to the substitution pattern. While phenylethylketone displays an enantioselectivity of 91%, the chemical yield was only 26%. Thus, the extension of this approach to the enantioselective preparation of a larger variety of 2,2-substituted oxiranes may be problematic, mostly because of ee loss in the first step and insufficient enantioamplification in the second.[51] A more general approach to optically active oxacycles may involve consecutive ring expansions of the respective optically active lower homologue via the reaction with **1** as the methylenation reagent. As this reaction proceeds via transition structure **2** and intermediate betaine **3**,[28] leaving the stereogenic center untouched, complete retention of the configuration of the product **4** is expected (Scheme 1). This approach may be useful for the construction of larger rings, i.e., the hitherto unknown methylenation of oxetanes to oxolanes ($n = 1$).

As part of developing novel ylide chemistry[53,54] we recently demonstrated[55] that upon the treatment of epoxides with an excess of **1** small amounts of oxolanes form, demonstrating the

(15) Balsamo, A.; Crotti, P.; Ferretti, M.; Macchia, F. *J. Org. Chem.* **1975**, *40*, 2870–2874.
(16) Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *8*, 2633–2643.
(17) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314–4347.
(18) Tang, Y. Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X. Z. *J. Antibiot.* **2000**, *53*, 934–943.
(19) Ishida, T.; In, Y.; Nishii, M.; Minami, Y. *Chem. Lett.* **1994**, 1321–1322.
(20) Dillon, N. P.; Lee, N. C.; Stappenbeck, F.; White, J. D. *J. Chem. Soc., Chem. Comm.* **1995**, 1645–1646.
(21) de Vivar, A. R.; Pérez, A.-L.; Arciniega, A.; Vidales, P.; Gaviño, R.; Villaseñor, J. L. *Tetrahedron* **1995**, *51*, 12521–12528.
(22) Perez-Castorena, A. L.; Arciniegas, A.; Castro, A.; Villasenor, J. L.; Toscano, R. A.; de Vivar, A. R. *J. Nat. Prod.* **1997**, *60*, 1322–1325.
(23) Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581–4609.
(24) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779–4807.
(25) Welch, S. C.; Rao, A. S. C. P.; Lyon, J. T.; Assercq, J.-M. *J. Am. Chem. Soc.* **1983**, *105*, 252–257.
(26) Sasaki, T.; Shimizu, K.; Masatomi, O. *Chem. Pharm. Bull.* **1984**, *32*, 1433–1440.
(27) Hintzer, K.; Koppenhoefer, B.; Schurig, V. *J. Org. Chem.* **1982**, *47*, 3850–3854.
(28) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133–5134.
(29) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
(30) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
(31) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.
(32) Wang, K.; Mayer, J. M. *J. Org. Chem.* **1997**, *62*, 4248–4252.
(33) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948–2953.
(34) Shu, L.; Shen, Y.-M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963–4965.
(35) Pirkle, V. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 2080–2082.
(36) Ohta, H.; Tetsukawa, H. *Agric. Biol. Chem.* **1979**, *43*, 2099–2104.
(37) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491–492.
(38) Yang, D.; Wong, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311–11312.
(39) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *92*, 968–969.
(40) Bentley, P. A.; Bergeron, S.; Cappi, M. C.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E. *J. Chem. Soc., Chem. Commun.* **1997**, 739–740.
(41) Porter, M. J.; Skidmore, J. *J. Chem. Soc., Chem. Commun.* **2000**, 1215–1225.
(42) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289–6300.
(43) Enders, D.; Hecker, P.; Meyer, O. *Tetrahedron* **1996**, *52*, 2909–2924.
(44) Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann. Chem.* **1997**, *6*, 1101–1113.
(45) Elston, C. L.; Jackson, R. F. W.; Macdonald, S. J. F.; Murray, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410–412.
(46) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725–2732.
(47) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430–1433.
(48) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *41*, 5620–5623.
(49) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748.
(50) Bertolini, F.; Crotti, S.; di Bussolo, V.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **2008**, *73*, 8998–9007.
(51) Sone, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1677–1680.
(52) Sone, T.; Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 10078–10079.
(53) Kiriy, A. V.; Yurchenko, A. G.; Fokin, A. A. *Zh. Org. Khim.* **2002**, *38*, 471–472.
(54) Fokin, A. A.; Kushko, A. O.; Kirij, A. V.; Yurchenko, A. G.; Schleyer, P. v. R. *J. Org. Chem.* **2000**, *65*, 2984–2995.
(55) Butova, E. D.; Fokin, A. A.; Schreiner, P. R. *J. Org. Chem.* **2007**, *72*, 5689–5696.

SCHEME 2. Oxirane (5), Oxetane (7), and Oxolane (9) Ring Expansions with 1[a]



[a]Relative ΔH_{298} at MP2/6-31+G(d), PCM, DMSO in kcal mol^{-1}, critical bond distances in Å.

feasibility of consecutive nucleophilic ring expansions with **1**. The synthetic potential as well as the mechanism and stereochemistry of this transformation still remains unexplored. Herein we present experimental and computational results on the consecutive expansions of cyclic ethers with **1** as the methylenation agent. We have also studied experimentally the regio- and stereospecificity of the epoxide and oxetane ring expansions with **1** to estimate their potential for the preparation of optically active oxetanes and oxolanes.

Results and Discussion

First we computed[56] the consecutive ring expansions with **1** involving highly polarized transition structures and betaines. Since conventional gas-phase DFT and MP2 methods overestimate the energies of such structures,[57] we employed a polarizable continuum model (PCM) to account for solvent effects.[58] This solvation model was previously successfully used[59] for the parent Corey−Chaykovsky reaction of **1** with carbonyl compounds.[60] We used DMSO as the solvent for both our computational modeling and the experiments. The attack of **1** on oxirane (**5**, Scheme 2) through **TS1** is associated with a 17.5 kcal mol^{-1} barrier, which is in line with the experimental observation that only moderate heating is required;[61] the gas phase computed barrier is much higher (30.1 kcal mol^{-1}). The ring opening is exothermic leading to betaine **6**; elimination of DMSO through low-energy **TS2** gives oxetane (**7**). The ring expansion occurs via S_N2-backside attack of **1** on the CH_2−O fragment (the barrier for the frontside attack is ca. 30.1 kcal mol^{-1} higher). Despite only a small ring strain release,[62] the overall transformation of **1** to **7** is highly exothermic (ΔH_{298} = −52.2 kcal mol^{-1}). This large driving force arises mainly from (i) the methylene transfer from the ylide into the oxacycle and (ii) the large increase in solvation energy in going from **1** to betaine **6**. Indeed, the gas-phase reaction (**1** + **5** → **6**) is +18.5 kcal mol^{-1} endothermic, emphasizing the importance of including the solvent in the computations.

The barrier for the attack of **1** onto **7** increases by ca. 8 kcal mol^{-1} (**TS3**); DMSO loss from betaine **8** through **TS4** is a fast process as both structures lie energetically below the reactants. The ring expansion of oxolane **9** with formation of

(56) Frisch, M. J. et al. Gaussian, Inc.: Pittsburgh, PA, 2004. For the details and the full reference see Supporting Information.
(57) Wei, Y.; Sateesh, B.; Maryasin, B.; Sastry, G. N.; Zipse, H. *J. Comput. Chem.* **2009**, *30*, 2617–2624.
(58) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117–129.
(59) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756.
(60) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
(61) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133–5134.
(62) Stirling, C. J. M. *Tetrahedron* **1985**, *41*, 1613–1666.

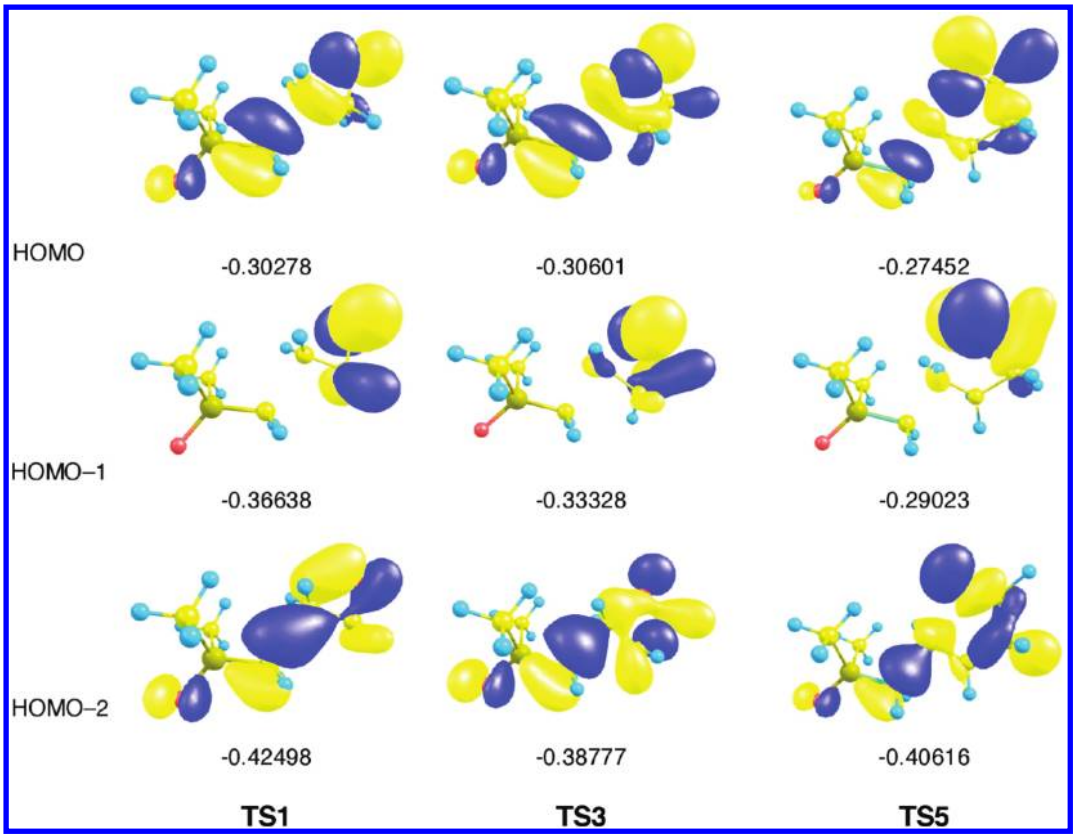


FIGURE 1. Selected orbital diagrams and energies for **TS1**, **TS3**, and **TS5**.

the six-membered oxane ring **11** through betaine **10** and **TS6** is hampered by the very large barriers for the initial attack (**TS5**, 38.0 kcal mol^{-1}). The results computed at MP2 deviate only slightly from the DFT barriers, which are 18.9, 28.2, and 39.2 kcal mol^{-1} through **TS1**, **TS3**, and **TS5**, respectively (PCM-B3PW91/6-31+G*).[63]

Thus, computations indicate a substantial increase in the barrier for the ring expansions of cyclic ethers from **5** to **7** and to **9**. This is due to decreasing contributions of the in-plane *p*-orbitals to the bonding between the reactants in the HOMO-2 of the transition structures **TS1**, **TS3**, and **TS5** (Figure 1). The overlap of these orbitals, that describes the newly forming C−C bond, decreases with increase of the ring size.

As expected, the methylenation of the epoxide ring is quite sensitive to the substitution pattern. This is apparent from the computations on the reaction of methyloxirane (**12**) with **1** (Scheme 3): the presence of the methyl group in **12** has no influence on the barrier for the attack on the CH_2 group (**TS7**, 17.2 kcal mol^{-1}, cf. **TS1**, 17.5 kcal mol^{-1}, Scheme 2), whereas the barrier for the attack on the tertiary carbon is much higher (**TS8**, 21.6 kcal mol^{-1}). Remarkably, in 2,2-disubstituted oxirane (**13**) the presence of another alkyl group decreases the barrier for the attack on the methylene carbon by 1.6 kcal mol^{-1} (**TS9**) relative to monomethyl derivative (**TS7**), presumably because of larger strain release in **TS9** versus **TS7**. As a consequence, the reactivity of 2,2-disubstituted oxiranes toward **1** must be higher than that of 2-monosubstituted substrates. Thus, our computations show that the ring expansions of oxacycles occur regioselectively and stereospecifically.

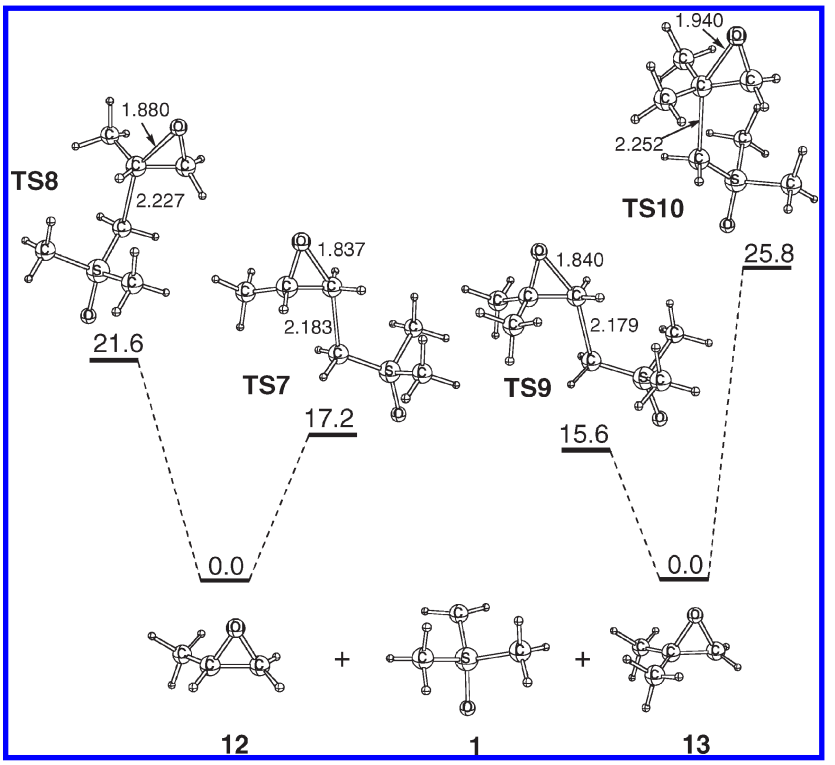
To verify our computational findings experimentally, we studied the methylenation of enantiopure (*R*)-2-phenyl- (**14**), (*R*)-2-(*n*-hexyl)- (**15**), (*R*)-2-benzyloxymethyl- (**16**), (*R*)-2-ethyl-2-phenyl- (**17**), and (2*R*,3*R*)-2-methyl-3-phenyl- (**18**) oxiranes (Table 1, entries 1−5). The reactions proceed smoothly in DMSO or *t*BuOH at 50−75 °C; **1** was prepared in situ from dimethylsulfoxonium iodide and sodium hydride or potassium *tert*-butylate (see Experimental Section for details). As a result we observed full conservation of the optical purity and retention of the stereochemistry was observed for the resulting oxetanes **19**−**22** (Table 1). In agreement with the computations the reactivity of **18** was too low to study the stereochemistry of the ring expansion as only trace amounts of product **23** were identified in the GC/MS analysis (Table 1, entry 5).

Our computations show that the ring expansion of oxetane **7** to oxolane **9** is accompanied by a ca. 26 kcal mol^{-1} barrier. As a consequence, we were able to achieve satisfactory conversions only upon heating to 125 °C. Oxetanes **24**−**32** were transformed to the respective oxolanes **33**−**41** in 56−91% preparative yields after 0.5−24 h representing a new general oxetane ring expansion reaction (Table 2, entries 1−9). The resulting oxolanes are stable in the presence of **1**; this agrees well with the high barrier computed for the attack of **1** onto **9** (Scheme 2).

We also tested the stereospecificity of the expansion of (*S*)-2-phenyloxetane (**19**) and (*S*)-*n*-hexyloxetane (**20**) and found complete conservation of the optical purity and

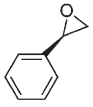
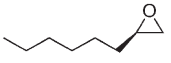
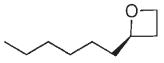
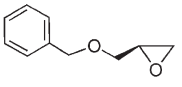
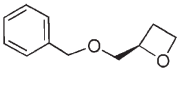
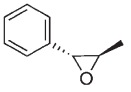
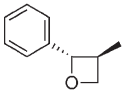
(63) We employed the method B3PW91, which is more trustworthy for energy evaluations than other DFT methods (see Schreiner, P. R.; Fokin, A. A.; Pascal, R. A.; A. de Meijere, *Org. Lett.* **2006**, *8*, 3635−3638).

SCHEME 3. Relative Barriers for the Attack of 1 on 2-Methyl-(12) and 2,2-Dimethyloxirane (13)[a]



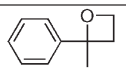
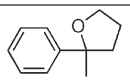
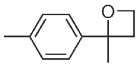
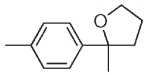
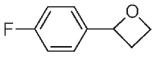
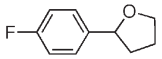
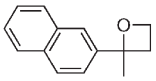
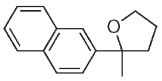
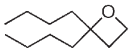
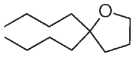
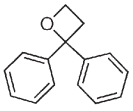
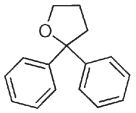
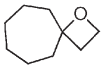
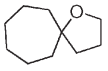
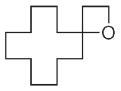
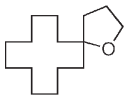
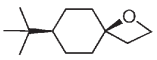
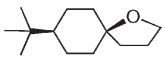
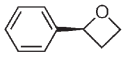
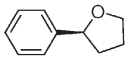
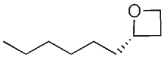
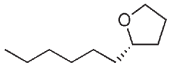
[a]Relative ΔH_{298} at MP2/6-31+G(d), PCM, DMSO in kcal mol^{-1}, critical bond distances in Å.

TABLE 1. Ring Expansions of Optically Active Oxiranes with 1 in DMSO

#	substrate	product	solvent, base (molar excess), temperature	yield, reaction time	*ee*,[a] %
1			DMSO, NaH (5), 70 °C	85%, 18 h	>98
	(*R*)-**14**	(*S*)-**19**			
2			*t*BuOH, *t*BuOK (2), 80 °C	91%, 18 h	>98
	(*R*)-**15**	(*R*)-**20**			
3			*t*BuOH, *t*BuOK (5), 80 °C	80%, 100 h	>98
	(*R*)-**16**	(*R*)-**21**			
4			DMSO, NaH (6), 110 °C	88%, 20 h	>98
	(*R*)-**17**	(*S*)-**22**			
5			*t*BuOH, *t*BuOK (5), 120 °C	traces, 120 h	n.d
	(2*R*,3*R*)-**18**	(2*S*,3*S*)-**23**			

[a]The stereochemistry was determined through the optical rotations in combination with GC on optically active stationary phase (SiHydrodex β-6-TBDM).

TABLE 2. Ring Expansions of Oxetanes with 1 in Diglyme (120−130 °C)

#	substrate	product	yield, reaction time
1	 **24**	 **33**	81%, 21 h
2	 **25**	 **34**	87%, 21 h
3	 **26**	 **35**	56%, 0.5 h
4	 **27**	 **36**	65%, 0.5 h
5	 **28**	 **37**	87%, 23 h
6	 **29**	 **38**	76%, 0.5 h
7	 **30**	 **39**	84%, 0.5 h
8	 **31**	 **40**	91%, 16 h
9	 **32**	 **41**	85%, 23 h
10	 (*S*)-**19**	 (*S*)-**42**	83%, 0.5 h ee>98%[a]
11	 (*S*)-**20**	 (*S*)-**43**	79%, 23 h ee>98%[a]

[a]The stereochemistry was determined through the optical rotations in combination with GC on optically active stationary phase (SiHydrodex *β*-6-TBDM).

stereochemistry of resulting oxolanes (*S*)- and (*R*)-**42** and (*S*)-**43** (Table 2, entries 10 and 11).

Conclusions

The methylenations of oxacycles with **1** occur via S_N2-type transition structures and are accompanied by fast elimination of DMSO. The expansion of the oxirane ring is associated with barriers of 15−17 kcal mol^{-1}, thus requiring only moderate heating; 2-alkyl- and 2,2-dialkyloxiranes are similarly reactive. The oxetane ring expansions require ca. 25 kcal mol^{-1} and take place at 120−130 °C to give oxolanes in high preparative yields. Asymmetric epoxides and oxetanes react with **1** regioselectively and stereospecifically. Full retention of enantiomeric purity and stereochemistry are observed for these nucleophilic ring expansions. Thus, this represents a new and general method for the preparation of optically active cyclic ethers from optically pure epoxides. Oxolanes are stable even under prolonged heating with **1** as the computed barriers for the ring expansion to the six-membered oxanes are too high.

Experimental Section

General Procedures for Oxirane Ring Expansions. Procedure A. To a well-stirred suspension of 0.038 g (1.6 mmol) of NaH in dry DMSO (5 mL) was added 0.352 g (1.6 mmol) of trimethylsulfoxonium iodide at room temperature. The mixture was gently heated to 50−70 °C, and 2-hexyloxirane (1 mmol) in DMSO (1 mL) was added in one portion. The reaction mixture was stirred at that temperature for 24−48 h, cooled, carefully quenched with water, and extracted three times with *n*-hexane. The combined extracts were washed with water and brine and dried over Na_2SO_4. Removal of the solvents gave the crude product, whose purification by chromatography (Al_2O_3, pentane−ether, 10:1) gave analytically pure oxetane **20** in 91% preparative yield.

Procedure B. To a well-stirred suspension of 0.226 g (2 mmol) of *t*-BuOK in dry *t*-BuOH (5 mL) was added 0.440 g (2 mmol) of trimethylsulfoxonium iodide at room temperature. The mixture was gently heated to 50−70 °C, and oxirane (1 mmol) in *t*-BuOH (1 mL) was added in one portion. The reaction mixture was stirred at that temperature for 15−72 h, cooled, carefully quenched with water, and extracted three times with *n*-hexane. The combined extracts were washed with water and brine and dried over Na_2SO_4. Removal of the solvents gave an oil, further purification as above gave pure oxetanes **19**, **21**, and **22** in 80−88% preparative yields (Table 1). The enantiomeric purity (>98%) was determined on GC HP6890 with Hydrodex-*β*-6TBDM stationary phase (25 m × 0.25 mm capillary column, 80−150 °C (1 °C/min), 150−250 °C (20 °C/min).

(*S*)-(−)-2-Phenyloxetane (19) through Procedure B[64]**.** ^{1}H NMR ($CDCl_3$, *δ*, ppm): 2.48−2.70 (m, 1 H), 2.85−3.09 (m, 1 H), 4.52−4.68 (m, 1 H), 4.69−4.87 (m, 1 H), 5.76 (m, 1 H), 7.18−7.49 (m, 5 H). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 30.7 (CH_2), 68.3 (CH_2), 82.9 (CH), 125.2 (CH), 127.8 (CH), 128.5 (CH), 143.6 (C). $[\alpha]_D = -38.0°$ (*c* 0.0329, $CHCl_3$). MS (*m*/*z*): 134 (12%), 104 (60%), 105 (100%), 106 (33%), 77 (40%), 51 (20%).

(*R*)-(+)-*n*-Hexyloxetane (20) through Procedure A[13]**.** ^{1}H NMR ($CDCl_3$, *δ*, ppm): 0.87 (t, *J* = 7 Hz, 3 H), 1.15−1.45 (m, 8 H), 1.52−1.58 (m, 2 H), 2.32 (m, 1 H), 2.62 (m, 1H), 4.50 (dt, 1H, *J* = 6.0, *J* = 8.0 Hz), 4.64 (dt 1H, *J* = 6 Hz, *J* = 8 Hz), 4.85 (pentet, 1H *J* = 7 Hz). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 14.6 (CH_3), 23.2 (CH_2), 24.6 (CH_2), 28.0 (CH_2), 29.8 (CH_2), 32.4 (CH_2), 38.6 (CH_2), 68.6 (CH_2), 83.4 (CH). $[\alpha]_D = +9.17°$ (*c* 0.0287 g/mL, $CHCl_3$). MS (*m*/*z*): 124 (7%), 113 (5%), 95 (10%), 81 (25%), 71 (100%), 67 (25%), 57 (20%), 55 (40%), 53 (5%).

(*R*)-(+)-2-Benzyloxymethyloxetane (21) through Procedure B[65]**.** ^{1}H NMR ($CDCl_3$, *δ*, ppm): 2.45−2.62 (m, 2 H), 3.23−3.60 (m, 2 H), 4.43−4.61 (m, 2 H), 4.51 (s, 2 H), 4.86−4.93 (m, 1 H), 7.12−7.29 (m, 5 H). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 23.9 (CH_2), 70.0 (CH_2), 73.4 (CH_2), 73.5 (CH_2), 81.2 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 138.3 (C). $[\alpha]_D = +4.7°$ (*c* 0.0090 g/mL,

(64) Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621–2634.
(65) Chakraborty, T. K.; Hussain, A. K.; Joshi, S. P. *Chem. Lett.* **1992**, *12*, 2385–2388.

$CHCl_3$). MS (*m*/*z*): 178 (1%), 107 (65%), 105 (20%), 92 (20%), 91 (100%), 79 (24%), 65 (35%), 57 (75%), 51 (24%).

(*S*)-(−)-2-Ethyl-2-phenyloxetane (22) through Procedure B[51]. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.84 (m, 3 H), 1.79−2.20 (m, 2 H), 2.60−2.96 (m, 2 H), 4.41−4.68 (m, 2 H), 7.16−7.49 (m, 5 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 7.5 (CH_3), 33.3 (CH_2), 36.0 (CH_2), 65.0 (CH_2), 89.3 (C), 124.2 (CH), 126.5 (CH), 128.0 (CH), 146.8 (C). $[\alpha]_D = -63.1°$ (*c* 0.0169 g/mL, $CHCl_3$). MS (*m*/*z*): 162 (7%), 132 (25%), 117 (45%), 105 (50%), 91 (45%), 77 (80%), 51 (100%).

General Procedure for Oxetane Ring Expansions. To a well-stirred suspension of 0.24 g (10 mmol) of NaH in dry diglyme (5 mL) was added 1.32 g (6 mmol) of trimethylsulfoxonium iodide at room temperature. The mixture was gently heated to 120−130 °C, and 1 mmol of oxetane in diglyme (1 mL) was added in one portion. The reaction mixture was stirred at 120−130 °C for 0.5−20 h, cooled, carefully quenched with water, and extracted three times with *n*-hexane. The combined extracts were washed with water and brine and dried over Na_2SO_4. Removal of solvent and purification by chromatography on silica gel (pentane−ether, 8:1) gave the respective oxolanes **33**−**43**, in 56−84% preparative yields (Table 2).

2-Methyl-2-phenyloxolane (33)[66,67]. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.50 (s, 3 H), 1.68−2.31 (m, 4 H), 3.83−4.10 (m, 2 H), 7.17−7.43 (m, 5 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 25.8 (CH_2), 29.7 (CH_3), 39.5 (CH_2), 67.6 (CH_2), 84.3 (C), 124.7 (CH), 126.3 (CH), 128.1 (CH), 148.2 (C). MS (*m*/*z*): 162 (1%), 147 (100%), 105 (90%), 91 (18%), 77 (54%), 51 (20%).

2-Methyl-2-(4-methylphenyl)oxolane (34). Colorless liquid. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.44 (s, 3 H), 1.60− 2.20 (m, 4 H), 2.25 (s, 3 H), 3.72−4.03 (m, 2 H), 7.00−7.10 (m, 2 H), 7.15−7.25 (m, 2 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 21.0 (CH_3), 25.8 (CH_2), 29.8 (CH_3), 39.4 (CH_2), 67.5 (CH_2), 84.1 (C), 124.6 (CH), 128.7 (CH), 135.8 (C), 145.1 (C). MS (*m*/*z*) 176 (5%), 161 (100%), 119 (98%), 91 (48%), 65 (24%), 51 (13%). HRMS (*m*/*z*): found 176.1203; calcd for $C_{12}H_{16}O$ 176.1201.

2-(4-Fluorophenyl)oxolane (35)[68]. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.65−1.78 (m, 1 H), 1.86−2.03 (m, 2 H), 2.16−2.31 (m, 1 H), 3.79−3.92 (m, 1 H), 3.98−4.07 (m, 1 H), 4.76−4.84 (m, 1 H), 6.89−7.02 (m, 2H), 7.16 − 7.28 (m, 2 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 26.0 (CH_2), 34.7 (CH_2), 68.6 (CH_2), 80.1 (CH), 115.0 (d, J = 21 Hz, CH), 127.2 (d, J = 8 Hz, CH), 139.0 (d, J = 2 Hz, C), 162.0 (d, J = 234 Hz, C). ^{19}F NMR ($CDCl_3$, δ, ppm, CBr_2F_2): −115.9 (s). MS (*m*/*z*): 166 (23%), 165 (30%), 123 (100%), 109 (40%), 95 (67%), 75 (60%), 50 (40%).

2-Methyl-2-naphtyloxolane (36). Colorless liquid. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.44 (s, 3 H), 1.62−2.36 (m, 4 H), 3.82−4.10 (m, 2 H), 7.29−7.50 (m, 3 H), 7.65−7.87 (m, 4 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 25.8 (CH_2), 29.6 (CH_3), 39.4 (CH_2), 67.7 (CH_2), 84.40 (C), 122.9 (CH), 123.8 (CH), 125.5 (CH), 126.0 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 132.3 (C), 133.2 (C), 145.5 (C). MS (*m*/*z*): 212 (21%), 197 (100%), 155 (75%), 127 (60%). HRMS (*m*/*z*): found 212.1206; calcd for $C_{15}H_{16}O$ 212.1201.

2,2-Di-*n*-butyloxolane (37)[69]. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.85−0.93 (m, 6 H), 1.04−1.50 (m, 12 H), 1.51−1.68 (m, 2 H), 1.70−1.90 (m, 2 H), 3.72 (*t*, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.1 (CH_3), 23.4 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 35.1 (CH_2), 38.3 (CH_2), 67.2 (CH_2), 84.9 (C). MS (*m*/*z*): 127 (100%), 85 (26%), 57 (58%).

2,2-Diphenyloxolane (38)[70]. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.76−2.00 (m, 2 H), 2.44 (*t*, J = 11 Hz 2 H), 3.92 (*t*, J = 11 Hz, 2 H), 7.04−7.46 (m, 10 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 25.6 (CH_2), 38.7 (CH_2), 67.5 (CH_2), 88.1 (C), 125.9 (CH), 126.85 (CH), 128.4 (CH), 146.6 (C). MS (*m*/*z*): 224 (56%), 165 (15%), 148 (15%), 147 (98%), 115 (18%), 105 (100%), 91 (14%), 77 (70%), 51 (24%).

1-Oxaspiro[4.6]undecane (39). Identical to the standard sample obtained earlier.[55]

1-Oxaspiro[4.11]hexadecane (40)[71]. Colorless liquid. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.27 (bs, 20 H), 1.46−1.62 (m, 4 H), 1.68−1.93 (m, 2 H), 3.70 (t, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 20.1 (CH_2), 22.2 (CH_2), 22.5 (CH_2), 25.6 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 33.1 (CH_2), 36.1 (CH_2), 66.4 (CH_2), 85.5 (C). MS (*m*/*z*): 224 (7%), 97 (100%), 84 (64%), 55 (43%). HRMS (*m*/*z*): found 224.2140; calcd for $C_{15}H_{28}O$ 224.2143.

7-*tert*-Butyl-1-oxaspiro[4.5]decane (41)[72]. Colorless liquid. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.8 (s, 9 H), 1.21−1.30 (m, 4 H), 1.49−1.58 (m, 5 H), 1.65−1.71 (m, 2 H), 1.77−1.86 (m, 2 H), 3.73 (*t*, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 23.8 (CH_2), 25.4 (CH_2), 27.7 (CH_3), 32.4 (C), 37.1 (CH_2), 38.2 (CH_2), 47.8 (CH), 66.7 (CH_2), 80.9 (C). MS (*m*/*z*): 196 (6%), 97 (100%), 84 (15%), 55 (25%). HRMS (*m*/*z*): found 196.1828; calcd for $C_{13}H_{24}O$ 196.1827.

(*S*)-(−)-2-Phenyloxolane (42)[73]. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.68−1.85 (m, 1 H), 1.9 −2.11 (m, 2 H), 2.22−2.34 (m, 1 H), 3.85−3.90 (m, 1 H), 4.00−4.07 (m, 1 H), 4.88−4.91 (m, 1 H), 7.2−7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$, δ, ppm): 26.1 (CH_2), 34.7 (CH_2), 68.7 (CH_2), 80.7 (CH), 125.7 (CH), 127.1 (CH), 128.3 (CH), 143.5 (C). MS (*m*/*z*): 148 (78%), 147 (100%), 117 (15%), 105 (80%), 91 (12%), 77 (20%); $[\alpha]_D = -37.6°$, (*c* 0.0162 g/mL, $CHCl_3$). The enantiomeric purity (> 98%) was determined on GC HP6890 with Hydrodex-β-6TBDM stationary phase (25 m × 0.25 mm capillary column, 80−150 °C (1 °C/min), 150−250 °C (20 °C/min). (*R*)-(+)-2-Phenyloxolane (**42**): yield 85%. $[\alpha]_D = +40.7°$ (*c* 0.0142 g/mL, $CHCl_3$).

(*R*)-(+)-*n*-Hexyloxolane (43)[70]. ^{1}H NMR: 0.81−0.91 (m, 3 H), 1.15−1.48 (m, 11 H), 1.77−2.08 (m, 3H, 3.62−3.94 (m, 3 H). ^{13}C NMR: 14.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 26.4 (CH_2), 29.4 (CH_2), 31.4 (CH_2), 31.9 (CH_2), 35.8 (CH_2), 67.7 (CH_2), 79.5 (CH); $[\alpha]_D = +3.98°$, (*c* 0.0061 g/mL, $CHCl_3$). MS (*m*/*z*): 156 (< 1%), 138, 71 (100%). The enantiomeric purity (> 98%) was determined on GC HP6890 with Hydrodex-β-6TBDM stationary phase (25 m x 0.25 mm capillary column, 80−150 °C (1 °C/min), 150−250 °C (20 °C/min).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, the Ministry of Science and Education of the Ukraine, and the Fonds der Chemischen Industrie.

Supporting Information Available: Copies of the NMR spectra, description of the theoretical methods, and XYZ coordinates of optimized species. This material is available free of charge via the Internet at http://pubs.acs.org.

(66) Frank, X.; Figadere, B.; Cave, A. *Tetrahedron Lett*. **1997**, *38*, 1413–1414.
(67) Hartung, J.; Schwarz, M.; Svoboda, I.; Fuess, H.; Duarte, M. T. *Eur. J. Org. Chem*. **1999**, 1275–1290.
(68) Hanson, R. L.; Banerjee, A.; Taha Comezoglu, F.; David Mirfakhrae, K.; Patel, R. N.; Szarka, L. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1925–1934.
(69) Fukuzawa, S.; Furuya, H.; Tsuchimoto, T. *Tetrahedron* **1953**, *52*, 1953–1960.
(70) Hansen, M. C.; Verdaguer, X.; Buchwald, S. L. *J. Org. Chem*. **1998**, *63*, 2360–2361.
(71) Weyerstahl, P.; Brendel, J.; Lutz, G. *Flavour Fragrance J*. **1992**, *7*, 1–7.
(72) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669–1675.
(73) Pirkle, W. H.; Spence, P. L. *J. Chromatogr., A* **1997**, *775*, 81–90.