Tetrahedron 65 (2009) 10791–10796

Contents lists available at ScienceDirect

Tetrahedron

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

Formal total synthesis of (±)-fragranol via template catalyzed 4-*exo* cyclization

Andreas Gansäuer *, Andreas Greb, Inga Huth, Dennis Worgull, Karsten Knebel

Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany

ARTICLE INFO

Article history:
Received 1 August 2009
Received in revised form 19 August 2009
Accepted 7 September 2009
Available online 12 September 2009

ABSTRACT

A novel approach to the synthesis of (±)-fragranol is described that relies on a radical 4-*exo* cyclization. This key step is catalyzed by a cationic titanocene complex with a pending amide ligand. In this manner the radical and its acceptor are bound to the titanocene center in a two-point mode. By this interaction the 4-*exo* cyclization that is not supported by *gem*-dialkyl substitution is rendered thermodynamically and kinetically favorable. Moreover, the crucial intermediates and transition structures become highly ordered. This results in a good diastereoselectivity of cyclobutane formation. From the key-intermediate, the formal total synthesis of the natural product can be completed in a few steps.

1. Introduction

The radical 4-*exo* cyclization has long been identified as one of the most difficult cyclization reactions. This is not only due to the high ring strain of the cyclobutane. Additionally, the ring-closure of the pentenyl radical is amongst the slowest radical reactions.[1] Moreover, it has even been challenged if this particular 4-*exo* cyclization is indeed kinetically favorable as suggested by Baldwin's rules.[2] Due to these limitations, 4-*exo* cyclizations are often too slow to maintain efficient chain propagation in classical free radical chemistry (Fig. 1).

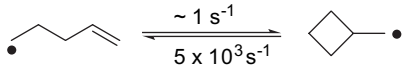

Figure 1. Kinetics of the cyclization of the 1-pentenyl radical and the opening of the cyclobutylcarbinyl radical at 298 K.

However, a number of synthetically important examples of the 4-*exo* cyclization have been reported that rely on special features. These include *gem*-dialkyl or *gem*-dialkoxyl substitution adjacent to the radical center and activation of the radical acceptors by conjugation with carbonyl groups.[3] Also, the 4-*exo* cyclization has been realized in a transannular manner.[4]

In the field of metal mediated radical chemistry the above-mentioned kinetic restrictions do not necessarily apply. Progress toward efficient 4-*exo* cyclizations has hence been successful. With SmI_2, the currently most popular electron transfer reagent, cyclizations with ketyl radicals and acrylates or vinylsulfones as radical traps result in the formation of cyclobutanols (Fig. 2).[5] The use of ketones as radical precursors may lead to undesired 5-*endo* cyclizations.[5c] However, the use of protic additives, such as water, can efficiently modulate the reactivity of SmI_2.[6]

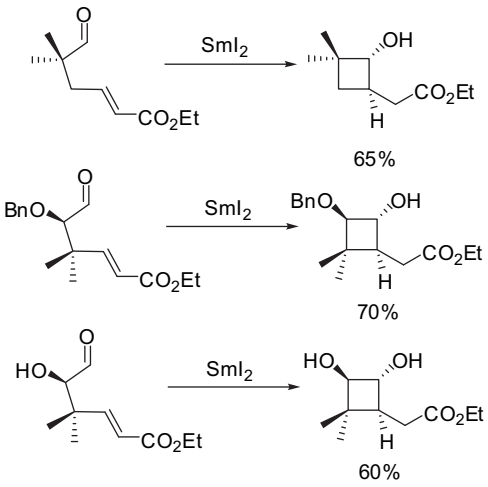

Figure 2. SmI_2-mediated 4-*exo* cyclizations.

The application of titanocene(III) chloride in radical chemistry constitutes a rapidly expanding field of research.[7] This is especially so for the radical generation from epoxides as introduced by Nugent and RajanBabu.[8] The structure of the reagent[9] and the mechanism of the ring opening have been established.[10] Recently, the catalytic variants of their reaction have become even more popular.[11] Important examples of rare reactions such as enantioselective radical generation[11d,h,r] or 3-*exo* cyclizations[11m,n] controlled by polarity

* Corresponding author. Tel.: +49 228 732800; fax: +49 228 734760.
E-mail address: andreas.gansaeuer@uni-bonn.de (A. Gansäuer).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.033

matching of radical reduction have been developed. A number of applications in the synthesis of complex molecules have emerged such as titanocene-catalyzed epoxypolyene cyclizations.[11k,o] Epoxide opening has also been used with excellent success for the initiation of the polymerization of styrene.[12] Other metal complexes have been proven to be less general, even though interesting methodology has been developed.[13]

In the field of the 4-*exo* cyclization, however, only isolated examples have been reported until recently. Fernández-Mateos and his group employed an aldehyde[14] and a nitrile[15] as radical trap to yield a cyclobutanol and a cyclobutanone, respectively, with Nugent's and RajanBabu's original protocol (Fig. 3).

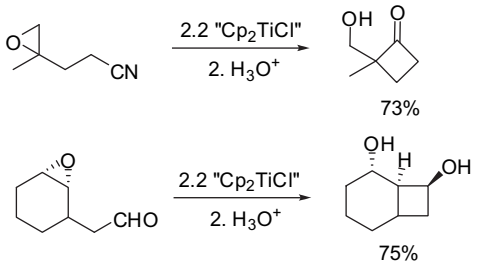

Figure 3. 4-*exo* cyclizations with aldehydes and nitriles stoichiometric in Cp_2TiCl_2.

A more general synthetic approach to cyclobutanes using titanocene catalyzed radical chemistry has been disclosed by us employing either α,β-unsaturated carbonyl compounds or nitriles as radical acceptors.[16] In many cases the use of alkyl substituted titanocenes is essential for the success of the reaction (Fig. 4), because in this manner the radicals can be rendered more persistent kinetically.

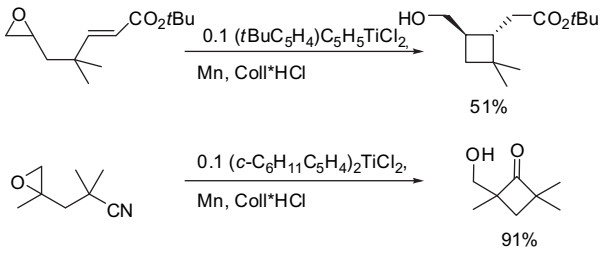

Figure 4. Titanocene catalyzed 4-*exo* cyclizations.

However, reactions with substrates lacking incorporation of the epoxide or the radical acceptor in additional rings or lacking *gem*-disubstitution in the tether between radical precursor and radical acceptor have, as yet, remained unsuccessful. This is a serious drawback, of course, because none of the described approaches is general enough to be used for all 4-*exo* cyclizations. Moreover, a synthetic solution relying on a substrate controlled course of the reaction should be of much broader significance for applications of radical cyclizations, because it can in principle be applied to other kinetically and thermodynamically difficult cyclizations, also.

Here, we present an approach to resolving this issue by introducing the concept of template catalysis to radical cyclizations. In the specific scenario (Fig. 5), the radical and the radical acceptor are both bound to a titanocene template. Ideal candidates for such templates are the cationic functional titanocenes that we have recently introduced.[17] These compounds have been demonstrated to bind the pending amide ligand reversibly. In this manner a vacant coordination site can be generated in situ for interactions with other molecules possessing polar functionality.

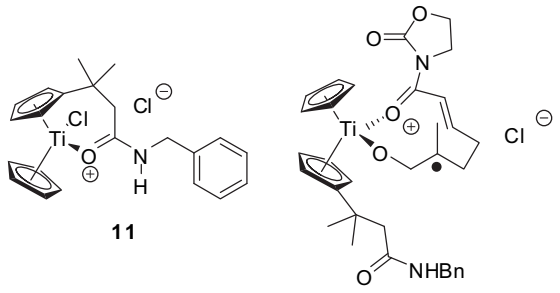

Figure 5. Concept of template catalyzed 4-*exo* cyclizations.

The desired two-point binding is to be realized through binding of the β-tinanoxy radical generated through reductive electron transfer and the pivotal coordination of titanium by a donor group displacing the amide ligand. To this end we chose an α,β-unsaturated oxazolidinone as the radical acceptor, because this polar functional group constitutes an excellent donor ligand for metals that should be able to replace the hemilabile pending amide ligand from titanium. This binding mode effectively renders the cyclization a transannular reaction and hence thermodynamically and kinetically favorable. Moreover, the tight binding of the substrate radical should also enforce a noticeable diastereoselectivity of the overall process. Additionally, the resulting products containing saturated oxazolidinones can be readily further manipulated, which is essential for a manifold of potential further applications.

We have chosen to highlight these attractive features of our novel reaction in the synthesis of (±)-fragranol (**1**).[18] This natural product constitutes a monoterpene first isolated from the roots of *Artemisia fragrans* Willd., that is shown in Figure 6. We are not aware of a synthetic approach to **1** that uses a stereoselective 4-*exo* cyclization for the construction of the cyclobutane ring. It should be noted that the highly stereoselective construction of cyclobutanes with three substituents at the adjacent carbon atoms has as yet not been achieved with radical based methodology.[16] The otherwise efficient use of substituted titanocenes[19] was of no use in this respect.

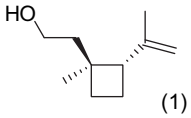

Figure 6. Fragranol, a monoterpene isolated from *Artemisia fragrans* Willd.

2. Results

Our retrosynthetic analysis of **1** is shown in Figure 7. The known alcohol **2** has been synthesized before by Knölker and has been transformed to **1** in three high yielding steps (oxidation to the

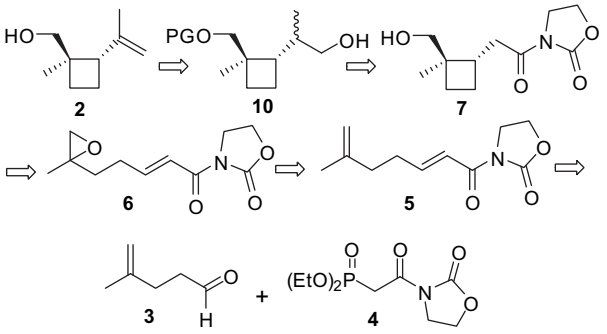

Figure 7. Retrosynthetic analysis of **1**.

aldehyde, homologization and reduction).[20b] Thus, our formal total synthesis of **1** is completed with the preparation of **2**.

The key step of our approach is constituted by the 4-*exo* cyclization of **6**, that is readily available in large quantities from aldehyde **3**[21] and phosphonate **4**[22] in a Horner–Wadsworth–Emmons reaction and epoxidation of **5** with mCPBA. Cyclobutane **7** can in principle be readily transformed into **2** via the sequence shown. After protection, methylation, and reduction **10** is obtained. Elimination of the hydroxyl group after activation and deprotection finally yields **2**.

The template catalyzed 4-*exo* cyclization of **6** required careful optimization. Our best conditions for the cyclization and the synthesis of **6** are shown in Figure 8.

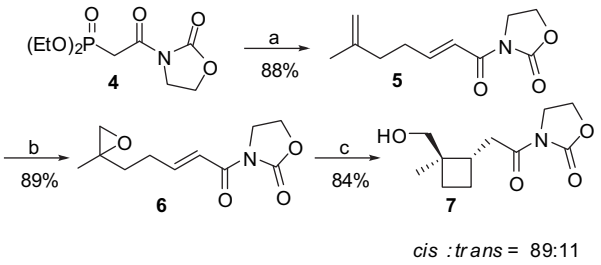

Figure 8. Synthesis of **6** and optimized conditions for its cyclization (Coll=2,4,6-trimethyl pyridine). Reagents and conditions: (a) NaH, THF, 30 min, **3**, 16 h, rt; (b) *m*CPBA, CH_2Cl_2, 16 h, rt; (c) 20 mol% **11**, 4.0 Mn, 5.87 Coll, 2.88 TMSCl, 44 h, rt (Coll=2,4,6-trimethyl pyridine).

The use of Cp_2TiCl_2 or alkyl substituted titanocenes that can be successfully employed in 4-*exo* cyclizations supported by the *gem*-dialkyl effect and in highly diastereoselective acrylate additions did not result in the formation of **7** at room temperature under any conditions. Also, the cationic titanocene **11** did not give any of the desired product under the protic conditions (Coll*HCl) that we have employed on many occasions, such as the catalytic reductive epoxide opening[11a,b,c] or in titanocene catalyzed pinacol couplings.[23] Presumably, this is due to product inhibition, because **7**, containing both a free hydroxyl group and an oxazolidinone, constitutes a potent ligand for the cationic and hence highly electrophilic catalyst.

Fortunately, Coll*Me_3SiCl, a reagent that was introduced by Oltra and Cuerva[11i,k,o] for mediating catalysis in titanocene promoted epoxypolyene cyclizations, yielded much better results. Under the conditions shown above, **7** could be isolated after desilylative work-up in a combined yield 84% in a diastereomeric ratio of 89:11. From this mixture the pure trans-isomer could be isolated in 71% when performing the reaction on a 0.5 mmol scale. When running the reaction with 2.6 mmol of substrate, the isolated yield of **7** is only slightly reduced to 69%.

We suggest that the superiority of the Coll*Me_3SiCl reagent is based on its ability to silylate the Ti–O bonds formed after the 4-*exo* cyclization. In this manner product inhibition is effectively prevented. Me_3SiCl that has been introduced by Fürstner[24] in mediating redox-catalysis cannot be used, because epoxides are opened by this reagent via S_N1 and S_N2 reactions, even though it has been successfully employed in titanocene catalyzed pinacol couplings.[25]

With a reliable and short access to **7** in hands we turned our attention to its conversion to **2**. The results of these investigations are summarized in Figure 9.

The conversion of **7** into tosylate **12** proceeded without difficulties. After almost quantitative silylation, the methylation yields **9** (relative configuration tentatively assigned) as a single isomer. Unfortunately, the other diastereoisomer could not be obtained pure and was hence discarded. After reduction with $LiAlH_4$, alcohol **10** was obtained in 82% yield.

The elimination to olefin **13** proceeded smoothly under reflux in glyme in the presence of 21.00 equiv of DBU. From **13** the known alcohol **2**[20b] was obtained in 81% yield by deprotection with TBAF.

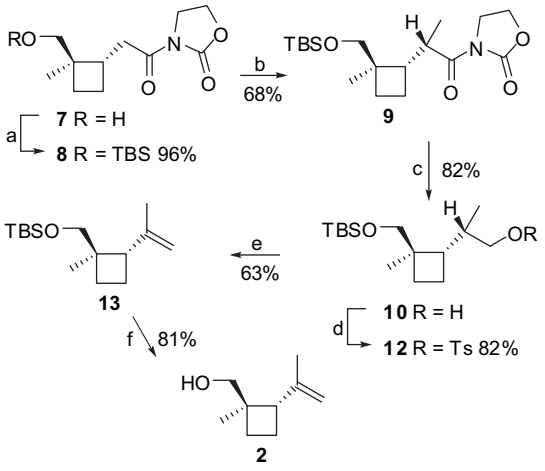

Figure 9. Completion of the synthesis of **2** from **7**. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 16 h, rt; (b) LDA, DMPU, −78 °C, 1 h, MeI, −78 °C→0 °C, 5 h; (c) $LiAlH_4$, Et_2O, 2 h, rt; (d) TsCl, pyridine, 72 h, rt; (e) DBU, NaI, glyme, 42 h, reflux; (f) TBAF, THF.

3. Conclusion

In conclusion, we have demonstrated that kinetically and thermodynamically difficult 4-*exo* cyclizations can be realized by template catalysis using our cationic titanocene complexes. The resulting reactions allow straightforward access to cyclobutanes pertinent to natural product synthesis in high diastereoselectivity. This was demonstrated in a formal total synthesis of (±)-fragranol.

4. Experimental section

4.1. General

All reactions were performed in oven-dried (100 °C) glassware under Ar. THF was freshly distilled from K. CH_2Cl_2 was freshly distilled from CaH_2. The products were purified by flash chromatography on Merck silica gel 50 (eluents given in brackets, EA refers to ethyl acetate, CH to cyclohexane) according to the procedure of Still.[26] Yields refer to analytically pure samples. Isomer ratios were determined by suitable ^1H NMR integrals of cleanly separated signals. NMR: Bruker DRX 300, AMX 300, AM 400; DRX500 ^1H NMR, $CHCl_3$ (7.26 ppm) or C_6D_5H (7.16 ppm) in the indicated solvent as internal standard in the same solvent; ^{13}C NMR, $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm) as internal standard in the same solvent; integrals in accordance with assignments, coupling constants are measured in Hz and always constitutes *J*(H,H) coupling constants. IR spectra: Perkin–Elmer 1600 series FTIR and Thermo Nicolet 380 as neat films on KBr plates or via ATR measurements. Mass Spectrometry: EI Thermoquest Finningan MAT 95 XL, calibration against PFK; ESI Bruker Daltonics microTOF-Q, calibration against HCO_2Na. Combustion analytics was performed on a vario micro cube from Elementar, Hanau.

4-Methylpent-4-enal **3**[21] and diethyl-2-oxo-2-(2-oxooxazolidin-3-yl)ethylphosphonate **4**[22] were prepared according to literature procedures.

4.2. Synthesis of 3-(6-Methyl-hepta-2,6-dienoyl)-oxazolidin-2-one (5)

Phosphonate **4**[22] (1.48 g, 5.50 mmol, 1.10 equiv) was added to a solution of NaH (60% in oil, 200 mg, 5.00 mmol, 1.00 equiv) in dry THF (20 mL) at rt. The mixture was stirred until it became a clear solution (30 min). The aldehyde **3**[21] (673 mg, 5.00 mmol, 1.00 equiv) was added over a period of 1 h and the solution was

stirred for 16 h. Water was added and the reaction mixture was extracted with Et_2O and EA. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (CH/EA 60:40) yielding **5** (922 mg, 4.41 mmol, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.25 (dt, J=15.3 Hz, J=1.2 Hz, 1H), 7.15 (dt, J=15.3 Hz, J=6.6 Hz, 1H), 4.75 (s, 1H), 4.71 (s, 1H), 4.41 (t, J=8.1 Hz, 2H), 4.06 (t, J=8.1 Hz, 2H), 2.43 (tdd, J=7.7 Hz, J=6.5 Hz, J=0.9 Hz, 2H), 2.20 (t, J=7.4 Hz, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=165.3, 153.6, 151.0, 144.3, 120.3, 110.9, 62.2, 42.8, 36.1, 30.8, 22.5; IR(ATR) ν=3085, 2965, 2925, 2360, 2340, 1760, 1475, 1385, 1335, 1170, 1040, 1010, 975, 885, 535 cm^{-1}; EIHRMS calcd for $C_{11}H_{15}NO_3$ [M] 209.1052, found 209.1053.

4.3. Synthesis of (*E*)-3-(5-(2-methyloxiran-2-yl)pent-2-enoyl)oxazolidin-2-one (6)

To a solution of **6** (1.80 g, 8.60 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at 0 °C, was added *m*CPBA (70% in H_2O, 1.56 g, 12.9 mmol, 1.50 equiv) in portions. The mixture was stirred for 16 h at rt. The solution was washed with K_2CO_3 (25% in H_2O), dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (CH/EA 50:50+1% NEt_3) yielding **6** (1.73 g, 7.60 mmol, 89%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ=7.60 (dt, J=15.4 Hz, J=1.6 Hz, 1H), 7.25 (dt, J=15.4 Hz, J=6.9 Hz, 1H), 3.03–3.00 (m, 4H, 4H), 2.17 (dq, J=4.9 Hz, J=0.6 Hz, 1H), 2.13 (d, J=4.9 Hz, 1H), 2.04–1.97 (m, 2H), 1.40 (t, J=7.7 Hz, 2H), 0.97 (d, J=0.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ=164.7, 153.5, 149.9, 120.9, 61.4, 55.6, 53.0, 42.4, 35.0, 28.3, 20.9; IR(ATR) ν=2920, 1765, 1680, 1630, 1475, 1385, 1355, 1290, 1270, 1200, 1110, 1040, 975, 895, 755, 705 cm^{-1}; ESIHRMS calcd for $C_{11}H_{15}NO_4Na^+$ $[M+Na]^+$ 248.0893, found 248.0889.

4.4. Synthesis of 3-(2-hydroxymethyl-2-methyl-cyclobutylacetyl)oxazolidin-2-one (7)

Strictly deoxygenated THF (3 ml) was added to a mixture of titanocene **11**[16] (48.0 mg, 100 μmol, 0.200 equiv) and Mn dust (110 mg, 2.00 mmol, 4.00 equiv) under Ar atmosphere and the suspension was stirred at rt until it turned green (about 15 min). Then, a solution of 2,4,6-collidine (355 mg, 2.93 mmol, 5.87 equiv) and epoxide **6** (113 mg, 500 μmol, 1.00 equiv) in THF (2 ml) was added and the mixture was stirred for 5 min. Me_3SiCl (156 mg, 1.44 mmol, 2.88 equiv) was added and the mixture was stirred at rt for 44 h. Phosphate buffer, KF (290 mg, 5.00 mmol, 10.0 equiv), TBAF (131 mg, 500 μmol, 1.00 equiv) and *tert*-butylmethylether were added and the suspension was stirred for 16 h. The solvent was removed and the solid residue extracted with Et_2O, EA and CH_2Cl_2. The solvent was removed and the residue was purified by flash chromatography (CH/EA 5:95) yielding the *cis*-**6** (10.3 mg, 13%) and the *trans*-**7** (85.5 mg, 71%) (84% combined yield, dr=89:11) as colorless oils. With 584 mg (2.6 mmol) of **6**, 405 mg of *trans*-**7** (69%) and 46 mg (8%) of *cis*-**7** were obtained in the same manner.

cis **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.40 (t, J=8.2 Hz, 2H), 3.99 (t, J=8.0 Hz, 2H), 3.77 (d, J=11.1 Hz, 1H), 3.45 (d, J=11.1 Hz, 1H), 3.18 (dd, J=17.1 Hz, J=8.7 Hz, 1H), 3.03 (dd, J=17.0 Hz, J=8.7 Hz, 1H), 2.59–2.45 (m, 1H), 2.10–2.04 (m, 1H), 1.93–1.70 (m, 2H), 1.69–1.57 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.8, 153.7, 67.4, 62.1, 42.6, 42.4, 38.9, 38.9, 28.5, 25.1, 22.3.

trans-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.41 (t, J=7.9 Hz, 2H), 3.99 (t, J=8.0 Hz, 2H), 3.58 (d, J=11.1 Hz, 1H), 3.31 (d, J=11.1 Hz, 1H), 3.06 (dd, J=18.6 Hz, J=9.9 Hz, 1H), 2.90 (dd, J=18.6 Hz, J=4.7 Hz, 1H), 2.57 (br s, O–H), 2.56 (ddt, J=15.6 Hz, J=8.0 Hz, J=4.5 Hz, 1H), 2.01–1.91 (m, 1H), 1.76–1.66 (m, 2H), 1.50–1.41 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=174.4, 153.6, 72.9, 62.2, 42.8, 42.6, 37.1, 35.7, 27.7, 21.5, 17.7; IR(ATR) ν=3430, 2928, 2865, 1760, 1690, 1480, 1385, 1335, 1220, 1100, 1020, 960, 760, 700, 625, 575 cm^{-1}; ESIHRMS calcd for $C_{11}H_{17}NO_4Na^+$ $[M+Na]^+$ 250.1050, found 250.1051.

4.5. Synthesis of 3-(2-[2-(*tert*-butyl-dimethyl-silanoxymethyl)-2-methyl-cyclobutyl])-acetyl-oxazolidin-2-one (8)

Imidazole (288 mg, 4.23 mmol, 3.00 equiv), *tert*-butyldimethylsilylchloride (637 mg, 4.23 mmol, 3.00 equiv) and DMAP (172 mg, 1.41 mmol, 1.00 equiv) were dissolved in DMF (5 mL) at 0 °C. Alcohol **7** (339 mg, 1.41 mmol, 1.00 equiv), dissolved in DMF (2 mL), was added dropwise to the reaction mixture and the suspension was stirred for 16 h at rt. Water was added and the crude mixture extracted with Et_2O and EA. The combined organic layers were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (CH/EA 60:40) yielding **8** (460 mg, 1.35 mmol, 96%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ=4.38 (t, J=8.1 Hz, 2H), 3.97 (t, J=8.4 Hz, 2H), 3.38 (d, J=15.3 Hz, 1H), 3.34 (d, J=15.3 Hz, 1H), 3.00 (dd, J=16.0 Hz, J=9.8 Hz, 1H), 2.90 (dd, J=16.0 Hz, J=7.1 Hz, 1H), 2.68–2.55 (m, 1H), 2.03–1.84 (m, 2H), 1.68–1.56 (m, 1H), 1.46–1.38 (m, 1H), 1.00 (s, 3H), 0.88 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.0, 153.7, 71.0, 62.9, 42.6, 42.6, 36.9, 34.4, 27.6, 26.1, 22.5, 22.4, 18.2, −5.28; IR(ATR) ν=2955, 2930, 2855, 1700, 1470, 1385, 1360, 1250, 1220, 1095, 835, 775 cm^{-1}; ESIHRMS calcd for $C_{17}H_{31}NO_4SiNa^+$ $[M+Na]^+$ 364.1920, found 364.1923.

4.6. Synthesis of 3-(2-[2-(*tert*-butyl-dimethyl-silanoyloxymethyl)-2-methyl-cyclobutyl]-propionyl)-oxazolidin-2-one (9)

To a solution of diisopropylamine (202 mg, 2.00 mmol, 2.00 equiv) in dry THF (12 mL) at 0 °C were added *n*-BuLi (2.5 M in hexane, 1.10 mL, 2.00 mmol, 2.00 equiv) and DMPU (1.5 mL). The solution was stirred for 30 min at 0 °C and cooled to −78 °C. Compound **8** (330 mg, 1.00 mmol, 1.00 equiv) was added and the mixture stirred for 1 h at −78 °C. MeI (4.26 g, 30.0 mmol, 30.0 equiv) was added and the reaction mixture was allowed to warm up to 0 °C for 6 h. NH_4Cl (aq) was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (CH/EA 60:40) yielding **9** (241 mg, 679 μmol, 68%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ=4.39 (t, J=8.3 Hz, 2H), 3.97 (t, J=8.1 Hz, 2H), 3.77 (m, 1H), 3.38 (d, J=9.8 Hz, 1H), 3.26 (d, J=9.6 Hz, 1H), 2.56–2.46 (m, 1H), 2.00–1.84 (m, 2H), 1.65–1.52 (m, 1H), 1.46–1.34 (m, 1H), 1.05 (d, J=6.6 Hz, 3H), 0.89 (s, 12H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=177.3, 153.2, 71.2, 61.9, 43.0, 42.4, 41.0, 39.2, 27.2, 26.1, 20.5, 18.5, 18.5, 15.8, −5.23; IR(ATR) ν=2955, 2930, 2855, 1780, 1700, 1680, 1460, 1385, 1360, 1330, 1250, 1215, 1090, 1040, 1220, 940, 775, 670 cm^{-1}; ESIHRMS calcd for $C_{18}H_{33}NO_4SiNa^+$ $[M+Na]^+$ 378.2071, found 378.2068.

4.7. Synthesis of 2-[(2-(*tert*-butyl-dimethyl-silanyl)-methoxy)-2-methyl-cyclobutyl]-propan-1-ol (10)

To a suspension of $LiAlH_4$ (17.6 mg, 465 μmol, 1.00 equiv) in dry Et_2O (5 mL) at 0 °C was added dropwise compound **9** (165 mg, 465 μmol, 1.00 equiv) in Et_2O (5 mL). The reaction mixture was stirred for 3 h at rt. NaOH (15% in H_2O), H_2O and again NaOH (15% in H_2O) was added and the crude mixture filtered. Removing the solvent yielded alcohol **10** (104 mg, 382 μmol, 82%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=3.55–3.45 (m, 1H), 3.52 (d, J=9.6 Hz, 1H), 3.34–3.29 (m, 1H), 3.38 (d, J=9.6 Hz, 1H), 1.91–1.84 (m, 2H), 1.69–1.50 (m, 3H), 1.33–1.25 (m, 1H), 1.14 (s, 3H), 0.91 (s, 9H), 0.64 (d, J=6.8 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=74.7, 68.1, 45.9, 42.5, 38.0, 27.7, 26.1, 21.6, 18.8, 18.7, 14.5, −5.3, −5.4; IR(ATR) ν=3370, 2955, 2930, 2855, 2360, 2340, 1460, 1385, 1360, 1255, 1075, 1030, 1005, 940, 815 cm^{-1}; ESIHRMS calcd for $C_{15}H_{32}O_2SiNa^+$ $[M+Na]^+$ 295.2069, found 295.2064.

4.8. Synthesis of 2-(2-((*tert*-butyldimethylsilyloxy)methyl)-2-methylcyclobutyl)propyl-4-methylbenzenesulfonate (12)

Alcohol **10** (138 mg, 507 μmol, 1.00 equiv) was dissolved in dry pyridine (2 mL) and *para*-toluenesulfonylchloride (193 mg, 1.01 mmol, 2.00 equiv) was added. The reaction mixture was stirred at rt for 72 h. After addition of H_2O the crude mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. Removing the solvent yielded **11** (178 mg, 418 μmol, 82%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=7.77 (d, J=8.3 Hz, 2H, H), 7.32 (d, J=7.8 Hz, 2H), 4.04 (dd, J=9.5 Hz, J=2.8 Hz, 1H), 3.50 (dd, J=9.6 Hz, J=8.8 Hz, 1H), 3.23 (d, J=15.7 Hz, 1H), 3.21 (d, J=15.7 Hz, 1H), 2.44 (s, 3H), 1.83–1.77 (m, 4H), 1.72–1.63 (m, 1H), 1.25 (t, J=9.3 Hz, 1H), 0.94 (s, 3H), 0.86 (s, 9H), 0.76 (d, J=5.9 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=144.6, 133.7, 129.9, 128.0, 74.6, 72.0, 42.7, 41.7, 34.7, 26.8, 26.2, 21.8, 21.0, 18.6, 17.6, 14.3, −5.31; IR(ATR) ν=2950, 2930, 2360, 1460, 1360, 1250, 1175, 1100, 950, 835, 810, 775, 670, 555 cm^{-1}; ESIHRMS calcd for $C_{22}H_{38}O_4SSiNa^+$ $[M+Na]^+$ 449.2152, found 449.2156.

4.9. Synthesis of *tert*-butyldimethyl((1-methyl-2-(prop-1-en-2-yl)cyclobutyl)methoxy)silane (13)

Compound **12** (178 mg, 418 μmol, 1.00 equiv) was dissolved in DME (2 mL) and NaI (197 mg, 1.32 mmol, 3.00 equiv) and DBU (134 mg, 882 μmol, 2.00 equiv) were added. The reaction mixture was refluxed for 42 h. The solvent was removed and the crude mixture was filtered through a short pad of silica (eluent: pentane). Removing the solvent yielded **12** (67 mg, 264 μmol, 63%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ=4.83 (br s, 1H), 4.64 (br s, 1H), 3.37 (s, 2H), 2.81 (t, J=8.7 Hz, 1H), 2.03–1.96 (m, 3H), 1.63 (s, 3H), 1.30–1.20 (m, 1H), 0.91 (s, 9H), 0.87 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=146.4, 109.4, 71.0, 44.8, 44.4, 26.3, 26.1, 23.3, 18.9, 18.5, 17.5, −5.2, −5.3; IR(ATR) ν=2955, 2855, 1460, 1255, 1090, 885, 835, 810, 775, 665 cm^{-1}; EIHRMS calcd for $C_{11}H_{21}OSi^+$ $[M-C(CH_3)_3]^+$ 197.1362, found 197.1363.

4.10. Synthesis of (2-isopropenyl-1-methyl-cyclobutyl)-methanol (2)[20b]

TBAF (116 mg, 370 μmol, 2.00 equiv) was added to a solution of **12** (47.0 mg, 185 μmol, 1.00 equiv) in THF (1 mL) and the mixture was stirred at rt for 23 h. The solvent was removed. The residue was purified by flash chromatography (pentane/Et_2O 80:20) yielding **2** (21 mg, 150 μmol, 81%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ=4.95 (s, 1H), 4.63 (s, 1H), 3.53 (d, J=6.98 Hz, 1H), 3.46 (d, J=6.98 Hz, 1H), 2.72 (t, J=8.93 Hz, 1H), 1.74–2.05 (m, 4H), 1.63 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=145.5, 110.1, 71.7, 44.2, 29.9, 26.6, 23.2, 19.1, 17.3; IR(ATR) ν=3345, 2935, 2865, 2360, 2340, 1645, 1455, 1375, 1030, 885 cm^{-1}; EIHRMS calcd for $C_8H_{13}O_4^{\bullet}$ $[M-OCH_3]^+$ 109.1017, found 109.1017.

Acknowledgements

We are indebted to the SFB 624 ('Template-Vom Design chemischer Schablonen zur Reaktionssteuerung') for continuing generous support.

References and notes

1. For rate constants of the cyclobutylcarbinyl radical ring opening and the pentenyl cyclization, see: (a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083–1092; (b) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970–974; (c) Park, S.-U.; Varick, T. R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975–2978; (d) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765–10772.
2. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
3. (a) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719–6722; (b) Jung, M. E.; Marquez, R.; Houk, K. N. *Tetrahedron Lett.* **1999**, *40*, 2661–2664; For reviews, see: (c) Jung, M. E. *Synlett* **1999**, 843–846; (d) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
4. (a) Elliot, M. R.; Dhimane, A.-L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427–3428; (b) Dhimane, A.-L.; Aïssa, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3284–3286.
5. (a) Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, 1305–1309; (b) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913–4916; (c) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345–2347; (d) Edmonds, D. J.; Muir, K.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790–801; (e) William, D. B. G.; Blann, K. *Eur. J. Org. Chem.* **2004**, 3286–3291.
6. (a) Trepovich, J. A.; Balili, M. N.; Pintauer, T.; Flowers, R. A., II. *Angew. Chem., Int. Ed.* **2007**, *46*, 8160–8163; (b) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136–1137; (c) Taaning, R. H.; Lindsay, K. B.; Schiøtt, B.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2009**, *131*, 10253–10262.
7. (a) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788; (b) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465–475; (c) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556–5573; (d) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63–92; (e) Barrero, A. F.; Quilez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627–1641; (f) Gansäuer, A.; Justicia, J.; Fan, C.-A.; Worgull, D.; Piestert, F. *Top. Curr. Chem.* **2007**, *279*, 25–52.
8. (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562; (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525–4527; (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409; (d) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
9. (a) Enemærke, R. J.; Hjøllund, G. H.; Daasbjerg, K.; Skrydstrup, T. *C.R. Acad. Sci.* **2001**, *4*, 435–438; (b) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2004**, *23*, 1866–1874; (c) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864; (d) Enemærke, R. J.; Larsen, J.; Hjøllund, G. H.; Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2005**, *24*, 1252–1262; (e) Larsen, J.; Enemærke, R. J.; Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2006**, *25*, 2031–2036.
10. (a) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansaäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041–2044; (b) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371.
11. (a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101–103; (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859; (c) Gansäuer, A.; Bluhm, H. *Chem. Commun.* **1998**, 2143–2144; (d) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909–2910; (e) Gansäuer, A.; Pierobon, M. *Synlett* **2000**, 1357–1359; (f) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500–2520; (g) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206–3208; (h) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.—Eur. J.* **2003**, *9*, 531–542; (i) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935–1938; (j) Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687–3690; (k) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-López, J. L.; Valdivia, M.; Haıdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem.—Eur. J.* **2004**, *10*, 1778–1788; (l) Gansäuer, A.; Rinker, B.; Ndene-Schiffer, N.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Eur. J. Org. Chem.* **2004**, 2337–2351; (m) Gansäuer, A.; Lauterbach, T.; Geich-Gimbel, D. *Chem.—Eur. J.* **2004**, *10*, 4983–4990; (n) Friedrich, J.; Dolg, M.; Gansäuer, A.; Geich-Gimbel, D.; Lauterbach, T. *J. Am. Chem. Soc.* **2005**, *127*, 7071–7077; (o) Justicia, J.; Oller-Lopez, J. L.; Campana, A. G.; Oltra, J. E.; Cuerva, J. M.; Bunuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911–14921; (p) Gansäuer, A.; Rosales, A.; Justicia, J. *Synlett* **2006**, 927–929; (q) Gansäuer, A.; Justicia, J.; Rosales, A.; Worgull, D.; Rinker, B.; Cuerva, J. M.; Oltra, J. E. *Eur. J. Org. Chem.* **2006**, 4115–4127; (r) Gansäuer, A.; Fan, C.-A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484–3485; (s) Gansäuer, A.; Fan, C.-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916–6917; (t) Justicia, J.; Campaña, A. G.; Bazdi, B.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *Adv. Synth. Catal.* **2008**, *350*, 571–576; (u) Justicia, J.; Álvarez de Cienfuegos, L.; Estévez, R.; Paradas, M.; Lasanta, A. M.; Oller, J. L.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Tetrahedron* **2008**, *64*, 11938–11943.
12. (a) Asandei, A. D.; Moran, I. W. *J. Am. Chem. Soc.* **2004**, *126*, 15932–15933; (b) Asandei, A. D.; Moran, I. W. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 6028–6038; (c) Asandei, A. D.; Moran, I. W. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 6039–6047; (d) Asandei, A. D.; Moran, I. W. *J. Polym. Sci., Part A: Polym.*

Chem. **2006**, *44*, 1060–1070; (e) Asandei, A. D.; Chen, Y.; Moran, I. W.; Saha, G. *J. Organomet. Chem.* **2007**, *692*, 3174–3182; (f) Asandei, A. D.; Chen, Y.; Saha, G.; Moran, I. W. *Tetrahedron* **2008**, *64*, 11831–11838.
13. (a) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017–7026; (b) Hilt, G.; Bolze, P.; Kieltsch, I. *Chem. Commun.* **2005**, 1996–1997; (c) Hilt, G.; Bolze, P.; Harms, K. *Chem.—Eur. J.* **2007**, *13*, 4312–4325.
14. Fernández-Mateos, A.; Martin de la Nava, E.; Pascual Coca, G.; Ramos Silva, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607–610.
15. Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silva, A. I.; Rubio González, R. *Synlett* **2004**, 1011–1014.
16. (a) Gansäuer, A.; Lauterbach, T.; Geich-Gimbel, D. *Chem.—Eur. J.* **2004**, *10*, 4983–4990; (b) Friedrich, J.; Walczak, K.; Dolg, M.; Piestert, F.; Lauterbach, T.; Worgull, D.; Gansäuer, A. *J. Am. Chem. Soc.* **2008**, *130*, 1788–1796; (c) Gansäuer, A.; Piestert, F.; Huth, I.; Lauterbach, T. *Synthesis* **2008**, *21*, 3509–3515.
17. (a) Gansäuer, A.; Franke, D.; Lauterbach, T.; Nieger, M. *J. Am. Chem. Soc.* **2005**, *127*, 11622–11623; (b) Klawonn, T.; Gansäuer, A.; Winkler, I.; Lauterbach, T.; Franke, D.; Nolte, R. J. M.; Feiters, M. C.; Börner, H.; Hentschel, J.; Dötz, K. H. *Chem. Commun.* **2007**, 1894–1895; (c) Gansäuer, A.; Winkler, I.; Worgull, D.; Lauterbach, T.; Franke, D.; Selig, A.; Wagner, L.; Prokop, A. *Chem.—Eur. J.* **2008**, *14*, 4160–4163; (d) Gansäuer, A.; Winkler, I.; Klawonn, T.; Nolte, R. J. M.; Feiters, M. C.; Börner, H. G.; Hentschel, J.; Dötz, K. H. *Organometallics* **2009**, *28*, 1377–1382; (e) Gansäuer, A.; Winkler, I.; Worgull, D.; Franke, D.; Lauterbach, T.; Okkel, A.; Nieger, M. *Organometallics* **2008**, *27*, 5699–5707.
18. Bohlmann, F.; Zdero, C.; Faas, U. *Chem. Ber.* **1973**, *106*, 2904–2909.
19. (a) Gansäuer, A.; Bluhm, H.; Pierobon, M.; Keller, M. *Organometallics* **2001**, *20*, 914–919; (b) Gansäuer, A.; Rinker, B.; Barchuk, A.; Nieger, M. *Organometallics* **2004**, *23*, 1168–1171.
20. (a) Kim, D.; Lee, Y. K.; Jang, Y. M.; Kim, I. O.; Park, S. W. *J. Chem. Soc., Perkin Trans. 1* **1990**, *12*, 3221–3224; (b) Knölker, H.-J.; Baum, G.; Schmitt, O.; Wanzl, G. *Chem. Commun.* **1999**, 1737–1738; (c) Bernard, A. M.; Frongia, A.; Secci, F.; Delogu, G.; Ollivier, J.; Piras, P. P.; Salaun, J. *Tetrahedron* **2003**, *59*, 9433–9440.
21. Webb, R. F.; Duke, A. J.; Parson, J. A. *J. Chem. Soc.* **1961**, 4092–4095.
22. Dias, L. C.; Melgar, G. Z.; Jardim, L. Z. A. *Tetrahedron Lett.* **2005**, *46*, 4427–4431.
23. (a) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *73*, 2070–2071; (b) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, *9*, 1923–1927.
24. (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475; (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533–2534; (c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.
25. (a) Gansäuer, A. *Chem. Commun.* **1997**, 457–458; (b) Gansäuer, A. *Synlett* **1997**, 363–364; (c) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923–1927.
26. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.