Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2597–2601
Tetrahedron Letters

Lithium enolates from a (−)-quinic acid-derived cyclohexanone with a β-alkoxy leaving group: regioselective preparation and evaluation of enolate stability towards β-elimination

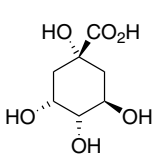
Lynne M. Murray, Peter O'Brien,* Richard J. K. Taylor and Stefan Wünnemann

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

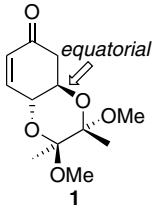
Received 11 October 2003; revised 18 January 2004; accepted 30 January 2004

Abstract—Deprotonation of a (−)-quinic acid-derived ketone {(2*S*,3*S*,4a*R*,8*R*,8a*S*)-8-[(*tert*-butyl(dimethyl)silyl)oxy]-2,3-dimethoxy-2,3-dimethylhexahydro-1,4-benzodioxin-6(5*H*)-one} using lithium hexamethyldisilazide (LHMDS) at −78 °C gave one regioisomeric enolate. The regiocontrol is governed by the axial β-silyloxy substituent and the resulting lithium enolate is stable towards β-elimination at temperatures up to −40 °C. It was found that the axial β-silyloxy group could be conveniently eliminated using 2.1 equiv of LHMDS at 0 °C for 1 h and that an equatorial β-alkoxy group was much more resistant to β-elimination. A chiral lithium amide base was used to overturn the inherent regioselectivity of ketone deprotonation with LHMDS.

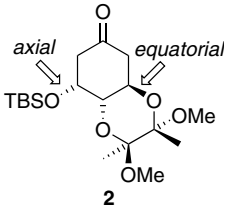
(−)-Quinic acid is a very useful and versatile chiral pool starting material for natural product synthesis[1] and many groups have developed elegant syntheses based on stereoselective reactions of (−)-quinic acid derivatives.[2] Highlights over the last few years include the preparation of some gabosines by Shinada et al.[3] and the total synthesis of (−)-brunsvigine by Sha et al.[4] Recently, we reported a range of highly stereoselective reactions of enone **1** (prepared in three steps from (−)-quinic acid) culminating in a new entry to the core of scyphostatin,[5] an inhibitor of neutral sphingomyelinase.



(−)-Quinic acid



1



2

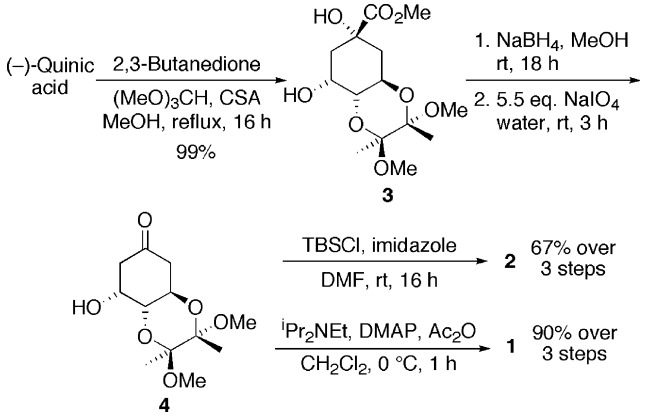
In our previous work, it was shown that the lithium enolate generated from **1** (by deprotonation with LHMDS) did not eliminate the potential β-alkoxy leaving group (equatorial orientation due to the conformational lock imparted by the Ley bis-ketal)[6] at −78 °C over 30 min. In a related study, we decided to investigate the deprotonation and subsequent elimination of ketone **2**, also prepared from (−)-quinic acid. Several interesting features are presented by studying ketone **2**: (i) being unsymmetrical, the *regioselectivity* of deprotonation needed to be determined and for regiocontrol, we imagined making use of chiral lithium amide bases;[7,8] (ii) the enolates generated from **2** possess either an *axial* β-silyloxy group or an *equatorial* β-alkoxy group allowing us to investigate stereoelectronic preferences for elimination in the same substrate and (iii) it was hoped that ketone **2** could itself become an established and useful synthetic intermediate if regio and stereoselective functionalisation processes could be developed. In this paper, we report our findings on the deprotonation and subsequent elimination of ketone **2**.

During the course of our work, full details of the preparation and characterisation of ketone **2** were reported by Whitehead and co-workers.[9] Based on their route, we modified our own methods and optimised a very convenient way of preparing multi-gram quantities of ketone **2**. First of all, (−)-quinic acid was converted into bis-ketal **3** (with concomitant methyl ester formation) in 99% yield (after chromatography). Then, methyl ester reduction using $NaBH_4$ in MeOH at room temperature (18 h) gave a 1,2-diol that was cleaved (*without*

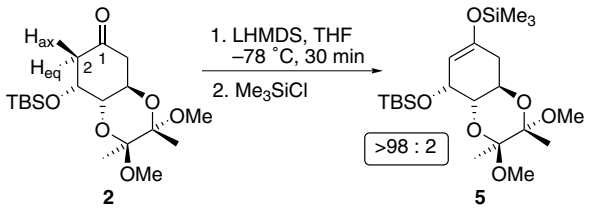
Keywords: Cyclohexanones; Deprotonation; Elimination reactions; Regiocontrol; (−)-Quinic acid.
* Corresponding author. Tel.: +44-(0)-1904-432535; fax: +44-(0)-1904-432516; e-mail: paob1@york.ac.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.01.148

isolation or work-up) to hydroxy ketone **4** after adding water and $NaIO_4$ (5.5 equiv) and stirring at room temperature for 3 h. Work-up generated crude hydroxy ketone **4** of high purity (as judged by ^1H NMR spectroscopy), which was TBS protected under standard conditions to give the desired ketone **2** {$[\alpha]_D^{20}$ +99.6 (*c* 1.0, CH_2Cl_2) (lit.,[9] $[\alpha]_D$ +93.5 (*c* 0.86, CH_2Cl_2))} in 67% yield (after purification by column chromatography) over the three steps from bis-ketal **3**. Instead of TBS protecting, crude hydroxy ketone **4** was also eliminated (using well documented conditions)[10] to give known[5,10] enone **1** {$[\alpha]_D^{20}$ +70.4 (*c* 1.0, CH_2Cl_2) (lit.,[10] $[\alpha]_D$ +64.4 (*c* 0.39, CH_2Cl_2))} in 90% overall yield from bis-ketal **3**. These protocols for preparing enone **1** and ketone **2** are the most convenient synthetic routes reported to date[11] and, by using Whitehead's $NaBH_4$ reduction of **3**, avoid the use of a problematic DIBAL-H reduction step.[5,10]



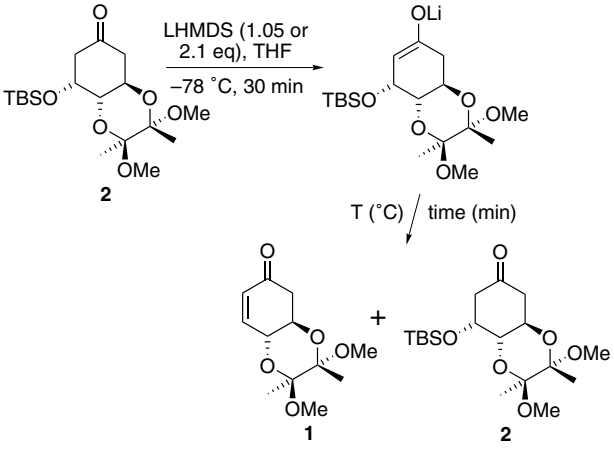
Initially, the regioselectivity of deprotonation of ketone **2** using LHMDS was determined. Treatment of a THF solution of ketone **2** with LHMDS at −78 °C for 30 min followed by enolate trapping with Me_3SiCl furnished a single silyl enol ether **5** in quantitative crude yield. The identity of **5** was established from its ^1H NMR spectrum (vide infra) and none of the regioisomeric silyl enol ether was generated under these conditions. The regioselectivity is presumably controlled by the acidifying effect on the C-2 proton H_{ax} by the axially disposed β-silyloxy group (antiperiplanar arrangement of the axial σC–H and axial σ*C–O orbitals). We have found one previous report of the use of an axial β-alkoxy group controlling the regioselectivity of deprotonation in a cyclohexanone (although not commented on by the authors): an axial β-silyloxy group led to complete regiocontrol of silyl enol ether formation in a route from D-glucose to (+)-calystegine B_2.[12] In this example, and in the generation of silyl enol ether **5**, it is notable that no elimination of the axial β-silyloxy group occurred. Similar results have been obtained by a number of groups using chiral bases at −78 °C in related systems.[7,13] However, of particular interest, Wipf et al. have reported that the enolates of cyclohexenones with a β-*N*-CO_2R group are only susceptible to elimination at temperatures above −20 °C.[14]



The regioselective preparation of a lithium enolate with an axial β-silyloxy group enabled a detailed investigation of the elimination process. Thus, we generated the lithium enolate by deprotonation of ketone **2** using LHMDS at −78 °C over 30 min.[15] The solution was then stirred at a particular temperature for a given length of time and quenched with saturated $NH_4Cl_{(aq)}$. After work-up, the crude reaction mixture was analysed by ^1H NMR spectroscopy to determine the amount of ketone **2** and enone **1** (elimination product). The full results are presented in Table 1. In all cases, the crude product mixture was obtained in essentially quantitative yield.

Initially, reactions were conducted using 1.05 equiv of LHMDS (entries 1–3). At −78 °C, the lithium enolate from **2** was stable to elimination of the β-silyloxy group for 1 h and probably much longer (entry 1). On raising

Table 1. Study on the deprotonation–elimination of ketone **2**



Entry	LHMDS (equiv)	*T* (°C)[a]	Time (min)[a]	**1**:**2**[b]
1	1.05	−78	60	0:100
2	1.05	−40	60	15:85
3	1.05	0	60	45:55
4	2.10	−78	60	2:98
5	2.10	−40	60	65:35
6	2.20	−40	90	75:25
7	2.20	−40	120	85:15
8	2.10	0	60	90:10
9	0.90	0	180	70:30

[a] The lithium enolate derived from ketone **2** was formed at −78 °C using LHMDS (equivalent indicated) and it was then stirred at *T* (°C) for a given time (min).

[b] The ratio of **1**:**2** was determined by ^1H NMR spectroscopy on the crude product mixture (essentially quantitative yield in each case).

the temperature (entries 2 and 3), we observed some β-elimination (up to 45% at 0 °C over 1 h, entry 3). Much more surprising was our observation when 2.10 or 2.20 equiv of LHMDS were utilised, as this led to considerably more β-elimination under otherwise identical conditions (compare entries 2 with 5 and 3 with 8). The highest amount of β-elimination (90%) was achieved with 2.10 equiv of LHMDS at 0 °C for 1 h (entry 8). Surprisingly, we were not able to force the β-elimination to completion using extended reaction times: some ketone **2** (up to 5–10%) always remained unaffected.

The conditions reported in entry 8 (2.10 equiv LHMDS, THF, 0 °C, 1 h) represent a new set of conditions for the elimination of an alkoxy group β to the carbonyl in a cyclohexanone and this could have synthetic utility.[16] Once the β-elimination has occurred, it seems likely that the excess LHMDS will deprotonate the enone **1** to give an enolate that appears to be resistant to further β-elimination at 0 °C. To verify this interesting result, enone **1** was deprotonated at −78 °C with LHMDS[15] (1.1 equiv, 30 min) and then stirred at 0 °C for 1 h. After quench and work-up, enone **1** was recovered unchanged in quantitative yield confirming that the lithium enolate from **1** is indeed stable to β-elimination under these conditions.

With ketone **2**, it is interesting that 2.10 equiv of LHMDS gives far more elimination compared to the use of 1.05 equiv. This may be due to the formation of an aggregate (e.g., a dimer between the lithium enolate and LHMDS)[17] in solution that favours β-elimination.[18] Speculating that the 0.05 equiv excess of LHMDS in the 1.05 equiv conditions (entries 2 and 3) may be catalysing the β-elimination process, we carried out a reaction with a deficiency of LHMDS (0.9 equiv) at 0 °C for an extended time of 180 min. In this case, 70% elimination occurred (entry 9) indicating that the lithium enolate from **2** is prone to β-elimination of the axial OTBS group at 0 °C even without an additional equivalent of LHMDS present. As described above, this is in contrast to the lithium enolate from **1**, which did not undergo elimination of the equatorial-alkoxy group at 0 °C.

In order to overturn the inherent regioselectivity of deprotonation presented by ketone **2**, our attention switched to the use of chiral bases. The regioselective preparation of silyl enol ethers using chiral lithium amide bases has previously been reported by Koga and co-workers[8a] and Simpkins and co-workers[8b] We selected chiral base (*S*)-**6**, originally introduced by Aoki and Koga,[19] as it is easy to synthesise the amine precursor,[20,21] it does not require the use of HMPA for high enantioselectivity and it performs well (up to 89% ee) even at −78 °C. In addition, based on Koga's results,[19] chiral base (*S*)-**6** should exhibit the required regioselectivity for removal of proton H_A (Fig. 1).

The deprotonation of ketone **2** using chiral base (*S*)-**6** was carried out under external and internal quench conditions. For externally quenched reactions, Simpkins and Majewski recommend the use of LiCl as an additive.[22] Thus, ketone **2** was deprotonated in THF at

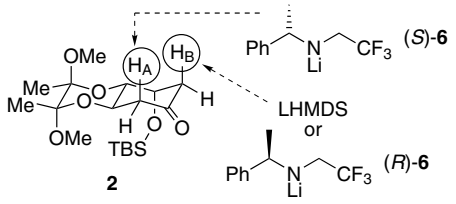
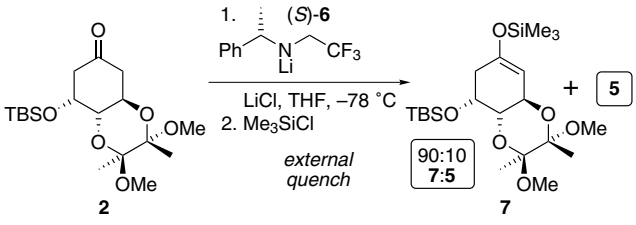


Figure 1.

−78 °C with 1.2 equiv of chiral base (*S*)-**6**/LiCl (generated from 1.2 equiv of the amine hydrochloride salt and 2.4 equiv of *n*-BuLi) for 30 min. Subsequent trapping with Me_3SiCl gave a 90:10 mixture of silyl enol ethers **7**[23] and **5** (by ^1H NMR spectroscopy) in crude quantitative yield, that is, a virtually complete reversal of regioselectivity was achieved. Essentially the same result (87:13 of **7** and **5**) was obtained under internal quench conditions.[24] In order to obtain silyl enol ethers **7** and **5** free from the chiral amine precursor to (*S*)-**6**, it was necessary to purify by column chromatography resulting in a 41% isolated yield of a 90:10 mixture of **7** and **5**. Thus, by using LHMDS or chiral base (*S*)-**6** regioselective access to synthetically useful silyl enol ethers **5** and **7**, respectively, was accomplished.



In summary, we have described different conditions for the regioselective generation of silyl enol ethers **5** and **7** from unsymmetrical (−)-quinic acid-derived ketone **2**. For example, chiral lithium amide base (*S*)-**6** was used to preferentially prepare silyl enol ether **7** from ketone **2**. In contrast, LHMDS deprotonation-trapping of **2** gave silyl enol ether **5** exclusively, presumably due to an activating effect of the β-silyloxy group. The lithium enolate derived from **2** and LHMDS (1.05 equiv) was completely stable to elimination of the β-silyloxy group at −78 °C for 1 h. However, at elevated temperatures some β-elimination was observed (e.g., 15 % at −40 °C and 45% at 0 °C; both over 1 h) and this process occurred to a much greater extent in the presence of 2.10 equiv of LHMDS. In contrast, the lithium enolate derived from enone **1** and 1.1 equiv of LHMDS did not eliminate the equatorial β-alkoxy group at 0 °C. These observations should prove useful for other researchers utilising β-functionalised cyclohexanones in organic synthesis.

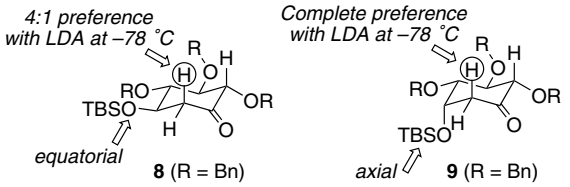
Acknowledgements

We thank the BBSRC and Hoffmann-La Roche for a CASE award (to L.M.M.), the EU for Erasmus funding

(of S.W.) and Prof. M. Majewski (University of Saskatchewan) for exchange of unpublished results.

References and notes

1. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3515–3545.
2. For recent examples, see: (a) Yoshida, A.; Ono, K.; Suhara, Y.; Saito, N.; Takayama, H.; Kittaka, A. *Synlett* **2003**, 1175–1179; (b) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619–622; (c) González, C.; Carballido, M.; Castedo, L. *J. Org. Chem.* **2003**, *68*, 2248–2255.
3. Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfune, Y. *Synlett* **2002**, 1341–1343.
4. Sha, C.-K.; Hong, A.-W.; Huang, C.-M. *Org. Lett.* **2001**, *3*, 2177–2179.
5. Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943–1946.
6. Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *Chem. Rev.* **2001**, *101*, 53–80.
7. For reviews, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1–26; (b) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439–1457.
8. (a) Sobukawa, M.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1990**, *1*, 295–298; (b) Bambridge, K.; Simpkins, N. S.; Clark, B. P. *Tetrahedron Lett.* **1992**, *33*, 8141–8144.
9. Begum, L.; Box, J. M.; Drew, M. G. B.; Harwood, L. M.; Humphreys, J. L.; Lowes, D. J.; Morris, G. A.; Redon, P. M.; Walker, F. M.; Whitehead, R. C. *Tetrahedron* **2003**, *59*, 4827–4841.
10. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166–173.
11. Our optimised routes to **1** and **2** start from **3** and proceed without purification of any of the synthetic intermediates. The protocol for the synthesis of ketone **2** is representative: (2*S*,3*S*,4a*R*,8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,3-dimethoxy-2,3-dimethylhexahydro-1,4-benzodioxin-6(5*H*)-one **2**: To a stirred solution of bis-ketal **3** (1.88 g, 5.9 mmol) in MeOH (25 mL) at 0 °C under N_2 was added $NaBH_4$ (1.61 g, 42.5 mmol) in portions. After effervescence had ceased, the mixture was allowed to warm to rt and stirred at rt for 18 h. Then, water (40 mL) and $NaIO_4$ (6.95 g, 32.5 mmol) were added and the resulting mixture was stirred at rt for 3 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (5×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude **4** as a white solid. To a stirred solution of crude **4** in DMF (13.5 mL) at rt under N_2 were added imidazole (1.54 g, 22.3 mmol) and *tert*-butyldimethylsilyl chloride (2.53 g, 16.7 mmol). The resulting mixture was stirred at rt for 16 h. Then, EtOAc (20 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic extracts were washed with 1 M $HCl_{(aq)}$ (20 mL) and saturated brine (3×20 mL). The organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude **2**. Purification by flash chromatography on silica with petrol–EtOAc (4/1) as eluent gave ketone **2** (1.48 g, 67%) as a white solid, mp 93–94 °C (lit.,[9] 100–101 °C); $[\alpha]_D^{20}$ +99.6 (*c* 1.0, CH_2Cl_2) (lit.,[9] $[\alpha]_D$ +93.5 (*c* 0.86, CH_2Cl_2)). Spectroscopic data was identical to that reported in the literature.[9]
12. Deprotonation of ketone **8** (with an equatorial β-silyloxy group) with LDA at −70 °C followed by reaction with



Me_3SiCl gave a 4:1 mixture of regioisomeric silyl enol ethers. In contrast, ketone **9** (with an axial β-silyloxy group) gave a single regioisomeric silyl enol ether under the same conditions. See: Boyer, F.-D.; Lallemand, J.-Y. *Tetrahedron* **1994**, *50*, 10443–10458.
13. (a) Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319–1322; (b) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207–208; (c) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1995**, 831–832; (d) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001–1004; (e) Hunt, K. W.; Grieco, P. *Org. Lett.* **2002**, *4*, 245–248; (f) Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry* **1997**, *8*, 181–184; (g) Honda, T.; Endo, K.; Ono, S. *Chem. Pharm. Bull.* **2000**, *48*, 1545–1548; (h) Honda, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2915–2919.
14. (a) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477–5480; (b) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739–742.
15. We are confident that the enolates from **1** and **2** form upon treatment with LHMDS at −78 °C for 30 min since they have been trapped with a range of aldehydes to give the expected aldol adducts in 23–80% yields.
16. For an example where others have previously encountered difficulty in eliminating a β-silyloxy group in a related cyclohexanone, see: Hareau, G.; Koiwa, M.; Hanazawa, T.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 7493–7496.
17. (a) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008; (b) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411.
18. An alternative explanation for the requirement of 2.10 equiv of LHMDS is as follows: if β-elimination of the enolate of **2** is slow and enone **1** is readily deprotonated then as enone **1** is formed, it could be deprotonated by the enolate of **2**. In this way, 2.0 equiv LHMDS would be required to complete the elimination process. We are grateful to a referee for this suggestion.
19. Aoki, K.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 2505–2506.
20. The amine precursor to (*S*)-**5** was prepared by (i) acylation of (*S*)-α-methylbenzylamine using $(CF_3CO)_2O$ and (ii) amide reduction using $BH_3{\cdot}Me_2S$. The hydrochloride salt of the amine was prepared by bubbling $HCl_{(g)}$ through a solution of the amine in Et_2O. Majewski, M. Personal communication.
21. (a) Aoki, K.; Koga, K. *Chem. Pharm. Bull.* **2000**, *48*, 571–574; (b) Pache, S.; Botuha, C.; Franz, R.; Kündig, E. P.; Einhorn, J. *Helv. Chim. Acta* **2000**, *83*, 2436–2451.
22. (a) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113–3116; (b) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465–5468.
23. ^1H NMR spectroscopic data for silyl enol ethers **5** and **7**: δ_H (400 MHz, $CDCl_3$) for **5**: 4.88 (dd, 1H, $J = 2.0, 6.0$ Hz), 4.25–4.15 (m, 2H), 3.46 (dd, 1H, $J = 3.5, 10.5$ Hz), 3.26 (s, 3H), 3.23 (s, 3H), 2.33 (dd, 1H, $J = 6.5, 16.5$ Hz, CH_AH_B), 2.21 (ddd, 1H, $J = 2.0, 10.5, 16.5$ Hz, CH_AH_B), 1.29 (s, 3H), 1.28 (s, 3H), 0.88 (s, 9H), 0.20 (s, 9H), 0.09 (s, 3H),

0.07 (s, 3H); δ_H (400 MHz, $CDCl_3$) for **7**: 4.76 (dd, 1H, $J = 2.0$, 2.0 Hz (app. t)), 4.58 (br d, 1H, $J = 9.0$ Hz), 4.07–4.04 (m, 1H), 3.49 (dd, 1H, $J = 2.0$, 9.0 Hz), 3.22 (s, 6H), 2.46 (br d, 1H, $J = 17.5$ Hz, CH_AH_B), 2.02 (ddd, 1H, $J = 2.0$, 2.0, 17.5 Hz (app. td), CH_AH_B), 1.29 (s, 3H), 1.27 (s, 3H), 0.89 (s, 9H), 0.20 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H). Analysis of the ^3J-values in the signals due to the CH_AH_B in each of **5** and **7** enabled the regioisomers to be identified. The ^3J-value of 10.5 Hz in the 2.21 ppm signal of **5** (due to one of the CH_AH_B protons) is consistent with a *trans*-diaxial coupling that is, the adjacent oxygen substituent must be equatorial; in the 2.46 and 2.02 ppm signals of **7** (due to the CH_AH_B protons), all ^3J-values are $\leqslant 2.0$ Hz and cannot be due to a *trans*-diaxial coupling that is, the adjacent oxygen substituent must be axial (OTBS group).

24. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495–498.