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Stereoselective synthesis of *anti*-1,3-diol units via Prins cyclisation: application to the synthesis of (−)-sedamine

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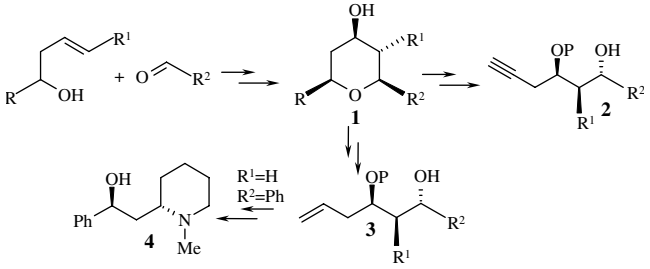
Abstract—The scope of the Prins cyclisation, the higher stereoselective synthesis of multisubstituted tetrahydropyrans from aldehydes and homoallylic alcohols, is expanded. A new approach for the stereoselective synthesis of polyketide precursors containing *anti*-1,3-diols, flanked by a variety of alkyl branches and functional groups is described. The approach is successfully exploited for the synthesis of (−)-sedamine.

1,3-Diol moieties occur as important subunits in a number of biologically active polyketide natural products and intermediates used for the synthesis of complex molecules.[1] Synthetic access to such subunits has long been a challenge for synthetic chemists, and a variety of methodologies have been developed for the synthesis of 1,3-diols.[2] Herein we report a diastereoselective and convergent approach to the synthesis of such moieties via highly stereoselective Prins cyclisation followed by reductive ring opening and have successfully utilised the method in the synthesis of an alkaloid, (−)-sedamine.

Prins cyclisation is effective and useful in the stereoselective synthesis of tetrahydropyrans (THPs),[3] with complex substitution patterns and has been successfully utilised in the synthesis of several natural products.[4] We recently developed a general route to β-hydroxy δ-lactones via Prins cyclisation[4a] and have begun to explore the potential of the reaction in the synthesis of acyclic frameworks useful in polyketide synthesis. In this report, we have further extended the scope of the Prins cyclisation to the synthesis of various polyketide precursors containing *anti*-1,3-diol units from a common pyran system **1** (Scheme 1). The salient features of our strategy are: synthesis of 1- or 6-pyranyl methanols from homoallylic alcohols and aldehydes and iodomethyl- or chloromethyl-mediated reductive opening of pyrans.



Scheme 1.

Scheme 2 depicts the synthesis of *anti*-1,3-diol motifs present in general structures **2** and **3**. Prins cyclisation using homoallylic alcohol **5** and various aldehydes resulted in multi substituted pyrans **7** in the presence of trifluoroacetic acid (TFA)[3a] in DCM followed by hydrolysis of the resulting crude trifluoroacetate with K_2CO_3 in MeOH. The predominant isomers were isolated by flash column chromatography and were found to have all substituents in equatorial positions.[3a,4a] The ^{1}H NMR spectra of the crude products showed 2–5% of other diastereomers.

Pyrans **7** were protected either as MOM ethers using MOM chloride, DMAP and DIPEA as base in DCM or TBS ethers using TBS chloride, DMAP and imidazole, followed by debenzylation using Na or Li in liquid NH_3 to obtain 6-pyranyl methanols **9**. Alcohols **9** on treatment with TPP, I_2 and imidazole in benzene gave iodo compounds **10** which on reductive opening with Zn in refluxing EtOH[5] delivered 1-alkenyl *anti*-4,6-diols **11**.

Keywords: Polyketide; 1,3-Diol; Prins cyclisation; Tetrahydropyrans.
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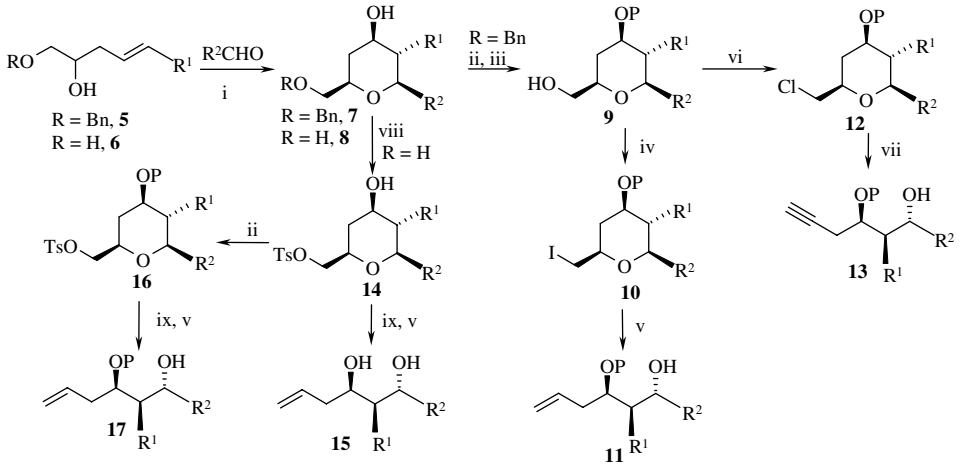


Scheme 2. Reagents and conditions: (i) TFA, rt, 2–3 h then K_2CO_3, MeOH, rt, 15 min (ii) MOMCl, Hunig's base, CH_2Cl_2 or TBSCl, imidazole, 0 °C–rt, 3–4 h (iii) Li or Na in liquid NH_3, 3–5 min (iv) TPP, I_2, imidazole, 0 °C–rt, 1–2 h (v) Zn, EtOH, reflux, 1 h (vi) TPP, $NaHCO_3$, CCl_4, reflux, 1 h (vii) $LiNH_2$, liquid NH_3, or LDA, −78 °C, 1–2 h (viii) TsCl, TEA, 0 °C–rt, 3–4 h (ix) NaI, acetone, reflux, 24 h.

Alternatively, pyranyl methanols **9**, when exposed to TPP and $NaHCO_3$ in refluxing CCl_4 produced chloro compounds **12** which on subjection to $LiNH_2$ or LDA underwent reductive opening[6] furnishing 1-alkynyl *anti*-4,6-diols **13**. The results are shown in Table 1.

Having succeeded in preparing partially protected *anti*-1,3-diol systems, we sought a route for the synthesis of unprotected *anti*-1,3-diols. To achieve this, we selected the homoallylic alcohol **6**, which on subjection to Prins cyclisation with several aldehydes produced diols **8**. The primary hydroxy group of **8** was tosylated using 1.1 equiv of tosyl chloride and TEA in DCM to produce **14**. Treatment of tosylates **14** with NaI in refluxing acetone gave the corresponding iodo compounds, which on treatment with Zn in refluxing ethanol underwent reductive opening to furnish **15** with both the hydroxy groups unprotected.

We also synthesised partially protected 1-alkenyl *anti*-4,5-diols in a similar way. After tosylation of the primary alcohol of **8**, the secondary alcohol was protected

Table 1. Synthesis of *anti*-1,3-diol frameworks via Prins cyclisation

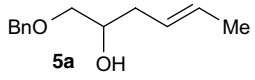
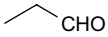
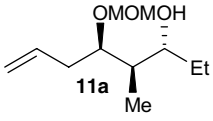
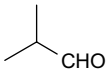
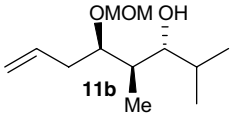
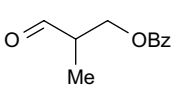
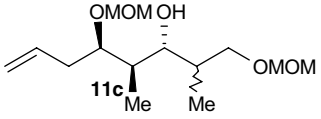
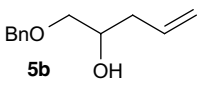
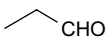
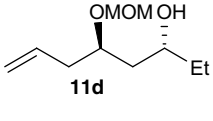
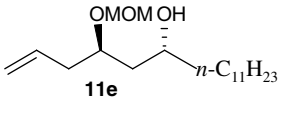
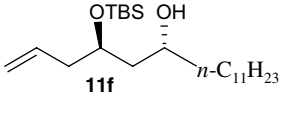
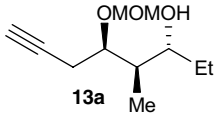
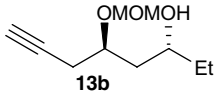
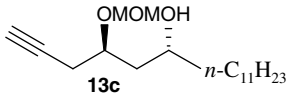
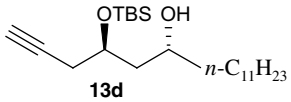
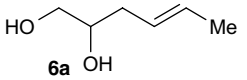
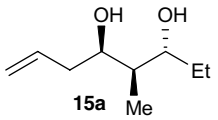
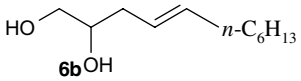
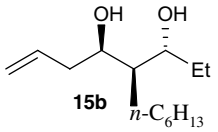
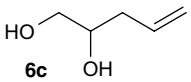
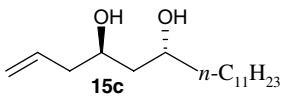
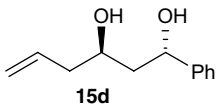
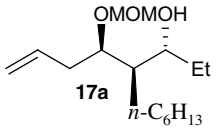
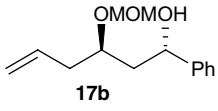
Homoallylic alcohol	Aldehyde	Product	Overall yield (%)
 **5a**		 **11a**	55
5a		 **11b**	53
5a		 **11c**	33
 **5b**		 **11d**	53
5b	*n*-$C_{11}H_{23}CHO$	 **11e**	50
5b	*n*-$C_{11}H_{23}CHO$	 **11f**	45

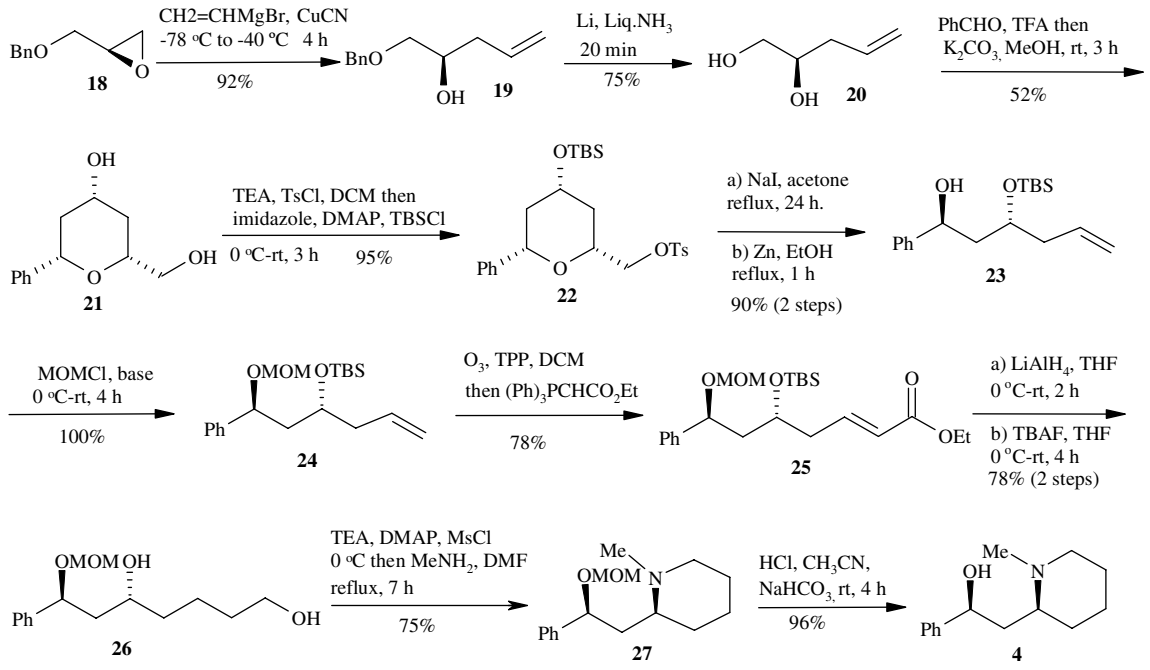
Table 1 (*continued*)

Homoallylic alcohol	Aldehyde	Product	Overall yield (%)
5a		 **13a**	35
5b		 **13b**	42
5b	n-$C_{11}H_{23}CHO$	 **13c**	40
5b	n-$C_{11}H_{23}CHO$	 **13d**	30
 **6a**		 **15a**	40
 **6b**		 **15b**	42
 **6c**	n-$C_{11}H_{23}CHO$	 **15c**	35
6c	PhCHO	 **15d**	38
6b		 **17a**	38
6c	PhCHO	 **17b**	35

either as its MOM ether or its TBS ether to give **16**, which, with NaI in refluxing acetone, afforded the corresponding iodo compound. Reductive opening with Zn in refluxing ethanol gave the partially protected 1,3-diol systems **17**. The results are summarised in Table 1. The homoallylic alcohols used were racemic and hence the products are racemic but diastereomerically pure. One could obtain the enantiomerically pure products by using enantiopure homoallylic alcohols.[3a,4a]

Finally, having established a general route for the stereoselective synthesis of *anti*-1,3-diol frameworks, we turned our attention to prove its practicality and thus extended the method to the synthesis of a piperidine alkaloid, (−)-sedamine **4**. Piperidine alkaloids constitute a large family of compounds, many of which exhibit a wide range of physiological activities, hence much effort has been devoted to the isolation and structure determination of such bases and to the development of general methodologies and routes for their synthesis.[7] Sedamine **4** was the first alkaloid isolated from *Sedum acre*[8] and was obtained later from a number of other *Sedum* species.[9] Both levorotatory (−)-sedamine and its enantiomer were found in all of the *Sedum* species mentioned above. Numerous syntheses of sedamine have been reported either in racemic form[10] or as a single enantiomer.[11]

Our synthesis, as summarised in Scheme 3, commenced from (*R*)-benzyl glycidyl ether **18**.[12] Reaction with



Scheme 3.

vinylmagnesium bromide in the presence of CuCN gave homoallylic alcohol **19**, which on treatment with Na or Li in liquid NH_3 underwent debenzylation producing diol **20**. Subjection of **20** and benzaldehyde to Prins cyclisation in the presence of TFA in DCM followed by hydrolysis of the resulting crude trifluoroacetate with K_2CO_3 in MeOH yielded trisubstituted pyran **21**. Tosylation with 1.1 equiv of tosyl chloride in the presence of TEA in DCM produced the corresponding primary tosylate which was protected in situ as TBS ether **22** by adding imidazole and TBS chloride to the reaction medium. Compound **22** on exposure to NaI in refluxing acetone gave the corresponding iodide which reacted with Zn in refluxing EtOH to furnish key intermediate **23** with the required *anti*-1,3-diol system. The newly created benzyl alcohol of **23** was protected as its MOM ether **24** in the presence of DIPEA and MOM chloride in DCM.

Ozonolytic cleavage of the olefinic bond of **24** followed by Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane gave α,β-unsaturated ester **25**. Reduction of ester **25** with LAH gave a saturated alcohol which upon exposure to TBAF in THF produced diol **26**. Diol **26** on treatment with mesyl chloride in the presence of TEA gave a dimesylate, which without purification was treated with methylamine in water in DMF at 50 °C resulting in the *N*-methyl piperidine **27** after sequential intermolecular and intramolecular substitutions.[13] MOM deprotection of **27** was simply carried out using HCl in acetonitrile and water at 50 °C for 4 h to furnish (−)-sedamine **4**, the data for which were in good agreement with the reported values.[14]

In conclusion, we have described a novel and versatile alternative for the synthesis of *trans*-1,3-diol frameworks through highly stereoselective Prins cyclisation and reductive ring opening of pyrans. Proving its practicality, the method was successfully utilised in a synthesis of an alkaloid, (−)-sedamine. Further applications of this methodology are in progress and the results will be disclosed in due course.

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References and notes

1. (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040; (b) Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306; (c) Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70*, 2225–2234; (d) Keck, G. E.; Truong, A. P. *Org. Lett.* **2005**, *7*, 2153–2156; (e) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644; (f) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527–529; (g) Li, C. R.; Sun, C. Y.; Su, C. G.-Q.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 4261–4264; (h) Amemiya, M.; Ueno, M.; Osono, M.; Masuda, T.; Kinoshita, N.; Nishida, C.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 536–540; Bialy, L.; Waldmann, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1748–1751; (i) Li, S.; Xiao, X.; Yan, X.; Liu, X.; Xu, R.; Bai, D. *Tetrahedron* **2005**, *61*, 11291–11298.
2. (a) Rychnovsky, S. D.; Powell, N. A. *J. Org. Chem.* **1997**, *62*, 6460–6461; (b) Obringer, M.; Colobert, F.; Neugnot, B.; Solladie, G. *Org. Lett.* **2003**, *5*, 629–633; (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501–504; (d) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889–8890; (e) Hunter, T. J.; O'Doherty, G. *Org. Lett.* **2001**, *3*, 1049–1052; (f) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403–405; (g) Grimaud, L.; Mesmay, R. de.;

Prunet, J. *Org. Lett.* **2002**, *4*, 419–421; (h) Yadav, J. S.; Srinivas, D. *Chem. Lett.* **1997**, 905–906, and references therein.

3. (a) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432; (b) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739–747; (c) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, *6*, 885–888; (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004**, *210*, 99–103; (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779–1783; (f) Zhang, W.-C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291–292; (g) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679–8682; (h) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191–198.
4. (a) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133–2136; (b) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485–3488; (c) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett.* **2005**, *7*, 2683–2686; (d) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217; (e) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407–3410; (f) Marumoto, S.; Jaber, J. J.; Vitale, J. P; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919–3922; (g) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755–758; (h) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686; (i) Kopecky, D. J.; Rychnoysky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8422; (j) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217–1219; (k) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022–3023.
5. (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016; For applications and modified procedures see: (b) Ferrier, R. J.; Furneaux, R. H.; Prasit, P.; Tyler, P. C.; Brown, K. L.; Gainsford, G. J.; Diehl, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1621–1628; (c) Ferrier, R. J.; Prasit, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1645–1648; (d) Ferrier, R. J.; Schmidt, P.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 301–304; (e) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069–2072; (f) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843–844; (g) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. S. *Tetrahedron* **2003**, *59*, 5333–5336.
6. (a) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett.* **1988**, *29*, 2737–2740; (b) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455–5458; (c) Yadav, J. S.; Deshpande, P.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046.
7. (a) Strunz, G. M.; Findlay, J. A. In *The alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89–174; (b) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31.
8. (a) Marion, L.; Lavigne, R.; Lemay, L. *Can. J. Chem.* **1951**, *29*, 347–351; (b) Granck, B. *Chem. Ber.* **1958**, *91*, 2803–2818.
9. (a) Logar, S.; Mesicek, M.; Perpar, M.; Seles, E. *Farm. Vestn.* **1974**, *21*; *Chem. Abstr.* **1975**, *82*, 82916h; (b) Krasnov, E. A.; Petrova, L. V.; Bekker, E. F. *Khim. Prir. Soedin.* **1977**, 585; *Chem. Abstr.* **1977**, *87*, 164249k.
10. (a) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1978**, *47*, 4647–4650; (b) Shono, T.; Matsumura, Y.; Tsubatta, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176; (c) Tirel, P. J.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 1947–1950; (d) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213–2219; (e) Ozawa, N.; Nakajima, S.; Zzoya, K.; Hamaguchi, F.; Nagasaka, T. *Heterocycles* **1991**, *32*, 889–894; (f) Driessens, F.; Hootele, C. *Can. J. Chem.* **1991**, *69*, 211–217; (g) Ghiaci, M.; Adibi, M. *Org. Prep. Proced. Int.* **1996**, *38*, 474.
11. (a) Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 63–74; (b) Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 43–58; (c) Schopf, C.; Cummer, G.; Wust, W. *Liebigs Ann. Chem.* **1959**, *626*, 134; (d) Wakabayachi, T.; Watanabe, K.; Kato, Y.; Saito, M. *Chem. Lett.* **1977**, 223; (e) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633–634; (f) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086–1093; (g) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525–1535; (h) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035–5036; (i) Poerwono, H.; Higashiyama, K.; Takahashi, H. *Heterocycles* **1998**, *47*, 262–270; (j) Yu, C. Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6665–6668; (k) Compere, C.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528–4532; (l) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982–1992; (m) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199; (n) Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danieli, B. *J. Org. Chem.* **2003**, *68*, 9525–9527; (o) Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *J. Org. Chem.* **2004**, *69*, 8514–8517.
12. Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *68*, 6776–6777.
13. (a) Mehta, G.; Reddy, M. S.; Thomas, A. *Tetrahedron* **1998**, *54*, 7865–7882; (b) Masaki, Y.; Oda, H.; Kozuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089–5092.
14. Selected physical data for compound **4**. Mp = 57–58 °C, lit.[11h] 58–60 °C; $[\alpha]_D^{20}$ −83.0 (*c* 1.40, EtOH), [lit.[11h] $[\alpha]_D^{20}$ −86.8 (*c* 1.10, EtOH)]; IR (KBr): ν_{max} 3357, 2932, 2855, 1451, 1363, 1061, 756, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20–7.42 (m, 5H), 4.89 (dd, 1H, $J = 10.6$, 2.6 Hz), 4.70 (br s, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 2.57 (m, 1H), 2.51 (s, 3H), 2.12 (m, 1H), 1.2–1.81 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 22.2, 25.9, 39.3, 39.8, 52.4, 61.2, 73.4, 125.4, 127.2, 128.3, 144.7. ESIMS: 220 $(M+1)^+$. HRMS *m*/*z* calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.1701, found 220.1738.