Tetrahedron Letters 56 (2015) 1825–1829

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Dibutyltin oxide mediated diastereoselective cyclodehydration/sulfonylation of 1,2,4-triols

Makhosazana P. Gamedze, Comfort M. Nkambule *

Department of Chemistry, Tshwane University of Technology, Private Bag X680, Pretoria 0001, South Africa

ARTICLE INFO

Article history:
Received 5 August 2014
Revised 31 January 2015
Accepted 18 February 2015
Available online 24 February 2015

Keywords:
Hydroxytetrahydrofuran
Cyclodehydration
Sulfonylation
1,2,4-Triols
gem-Disubstituent

ABSTRACT

Dibutyltin oxide (Bu_2SnO) mediated cyclodehydration or sulfonylation of 1,2,4-triols is predictably diastereoselective depending on the steric bulk of the substituents at C4. A larger difference (ΔA-value >1 kcal/mol) leads to the *syn*-1,2,4-triols favouring cyclodehydration (78–85%) to form 3-hydroxytetrahydrofurans, with the *anti*-1,2,4-triols favouring monosulfonylation (66–87%). Triols from symmetrical ketones preferentially undergo cyclodehydration in high yield (>75%) due to a *gem*-disubstituent effect. Thus, the 1,2,4-triols derived from simple cyclic ketones also favour cyclodehydration to form spirocyclic 3-hydroxytetrahydrofurans in 72–79% yields.

The tetrahydrofuran moiety is present in a wide array of natural products, most of which exhibit biological activities. Extensive work has been performed towards the construction of tetrahydrofurans encompassing a variety of designs, which have been summarized in a comprehensive review by Wolfe and Hay.[1] The most common strategies involve cyclodehydration of 1,4-diols,[2] cycloetherification via S_N2 displacement (O1→C4 or O4→C1) of leaving groups,[3] epoxide, selenoxide or aziridine ring opening,[4] iodo- or silyl-promoted cyclizations of unsaturated alcohols,[5] and nucleophilic addition of alkenes to oxonium ions.[6]

It is a general observation that in S_N2-like (O1→C4 or O4→C1) displacement reactions, any difference in rates is potentially due to the varying stabilities of diastereomeric transition states leading to the THF, due to eclipsing or staggered relationships between the incoming nucleophile and substituents close to the leaving group. In the reported cases the diastereomeric ratio is never greater than 4:1 and seems largely independent of the alkyl/aryl group at C4.[4d,7]

In 1985, Yoshida and co-workers reported the stereoselective synthesis of THFs from 4-pentene-1,3-diols where, at 0 °C, only the *syn*-1,3-diols reacted while the *anti*-1,3-diols remained unreactive.[5c] We have previously reported that 3-hydroxytetrahydrofurans are readily formed during the attempted tin-catalysed, mild sulfonylation of acyclic 1,2,4-triols.[8] Interestingly, we observed stereo dependency where the *syn*-1,2,4-triol isomers gave the *anti*-THF product exclusively, while the *anti*-1,2,4-triol isomers gave a mixture of the *anti*-2,4-diol monotosylate (major) and *syn*-THF (minor) products. We argued that the diastereoselectivity of the reaction could be explained by a double activation of the triol moiety by a tin acetal shift from the 1,2-diol to the 2,4-diol. This would form a six-membered Zimmerman–Traxler-like intermediate and the reaction should proceed via two energetically different diastereomeric boat conformer transition states **Ia** and **Ib** (Fig. 1). A similar boat transition state, based on hydrogen bonding between 1,3-diols was proposed by Yoshida and co-workers in the iodocyclization of 4-penten-1,3-diols;[9] we hypothesized that tin chelation of 1,3-diols should be stronger, and thus more influential than hydrogen bonding, and therefore would be a significant contributor to the reaction pathway.

In the proposed diastereomeric boat transition states (Fig. 1), it is clear that tin chelation of the 2,4-diol exacerbates the eclipsing steric effect in the *anti*-2,4-diol **Ib**, and thus would disfavour formation of the *syn*-THF. Therefore, in the dibutyltin oxide mediated cyclodehydration of 1,2,4-triols (Scheme 1), we anticipate that the larger the steric bulk differences (ΔA-value) between the two groups at C4 (R^1, R^2), then the greater would be the observed stereo dependency for *anti*-THF formation from *syn*-1,2,4-triols and the formation of the *anti*-2,4-diol tosylate from the *anti*-1,2,4-triols. Conversely, as the ΔA-value becomes smaller, we predict an increase in the ratio of the formation of the *syn*-THF from the *anti*-1,2,4-triols.

Overall, we postulate that the THF is the 'determined or preferred product' of the reaction of 1,2,4-triols, but that monosulfonylation is an incomplete reaction due to the tin-chelate

* Corresponding author. Tel.: +27 12 3826382; fax: +27 12 3826386.
E-mail address: Nkambulecm@tut.ac.za (C.M. Nkambule).

http://dx.doi.org/10.1016/j.tetlet.2015.02.083
0040-4039/

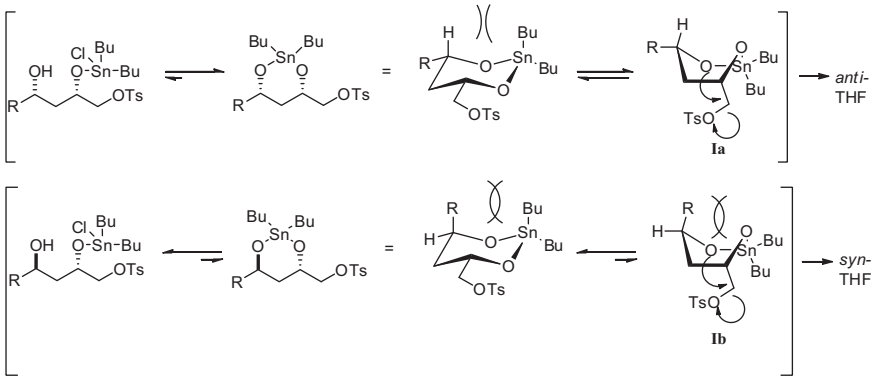
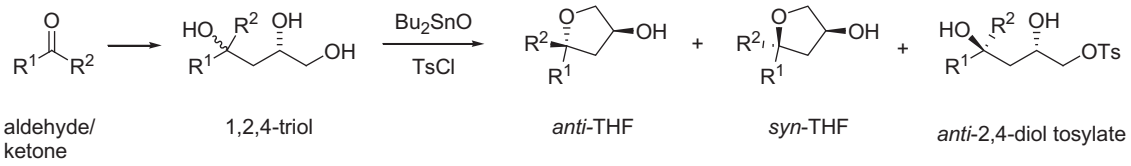


Figure 1. Proposed mechanism for the diastereoselective THF synthesis from 1,2,4-triols.



Scheme 1. General scheme for the cyclodehydration or sulfonylation of 1,2,4-triols.

induced thermodynamic barrier to cyclization for the *anti*-1,2,4-triols. This is contrary to the reported observation of cyclization as an unavoidable nuisance pathway (in quantitative yield) in the attempted tosylation of *anti*-1,2,4 triols.[10] In this Letter we report additional evidence for our proposed mechanism on the diastereoselectivity of the dibutyltin oxide mediated cyclodehydration or sulfonylation (CDS) method.

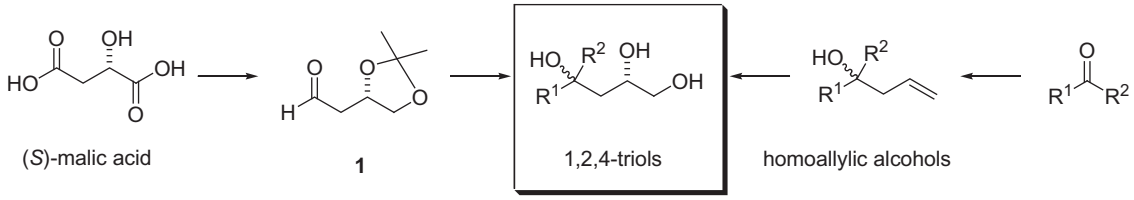
There are a plethora of methods for the preparation of 1,2,4-triols, including some elegant stereoselective methods for the synthesis and dihydroxylation of homoallylic alcohols and aldol condensations.[11] However, for the purposes of demonstrating the further reactions of 1,2,4-triols, we have restricted our approach to the direct Grignard alkylation of the diol aldehyde **1** derived from (*S*)-malic acid, and the dihydroxylation of homoallylic alcohols derived from the allylation of ketones and aldehydes (Scheme 2) according to reported methods.[12] The details of the synthesis and characterization of the 1,2,4-triols can be found in Supplementary material.

The diastereomers of the 1,2,4-triols synthesized (Fig. 2) were readily separated by column chromatography; in general the *syn*-triols are less polar and elute before the *anti*-triols. The overall yield of the triol diastereomers from aldehydes and ketones was very good and ranged from 39% to 55%. The relative stereochemistry of the triols was established by comparison (Δ ppm) of the ^{13}C NMR chemical shifts for the three C–O carbons (C1, C2 and C4) with previously reported characterizations. With the triols in hand, they were subjected to the dibutyltin oxide mediated CDS reaction conditions and the results are presented in Tables 1 and 2.[13]

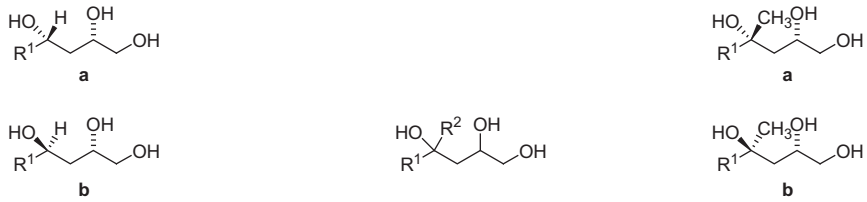
Our preliminary objective was to demonstrate that in the absence of a thermodynamic barrier, the proposed reaction conditions [Bu_2SnO (cat.), Et_3N (1 equiv), refluxing CH_2Cl_2] would lead to the cyclodehydration of the 1,2,4-triols. Hence, the reaction of 1,2,4-butanetriol (**2**), where the two groups at C4 are both hydrogens, was used as a test case (Table 1, entry 1). The exclusive and quantitative (98%) formation of 3-hydroxytetrahydrofuran confirmed our hypothesis and we set out to investigate the diastereoselectivity, and indeed, the stereodivergency of the method.

Our postulate was that as the steric size differences between the two groups at C4 increased (increasing Δ*A*-values), the ratio of the diastereomeric THFs (**c**:**d**) would also increase because the *syn*-triol diastereomers would form preferentially the *anti*-THFs (**c**), while the *anti*-triol diastereomers would form the monosulfonyl derivatives (**e**). Indeed, the results obtained showed that the *anti*-THFs (**c**) were formed in high yields (80–85%) for all the *syn*-triols, while the monotosylate (**e**) was the major product (66–87%) for all the *anti*-triols (Table 1, entries 2–11). As predicted, the diastereomeric ratio (**c**:**d**) increased from 7:1 to >99:1 as the Δ*A* value increased from 1.68 to 4.79 kcal/mol (Table 1, entries 2–11). In the case of 5,5-dimethyl-1,2,4-hexanetriols (**7a** and **7b**), formed from pivaldehyde, where the Δ*A*-value difference was the largest, the *syn*-THF (**7d**) was not observed at all. Our interpretation of this result is that for **7b** the barrier to cyclization is too high to be overcome (Table 1, entry 11).

On the other hand, when the Δ*A* value decreased to ~1 kcal/mol, as was the case for the triols **13a** and **13b**, the THF diastereomeric ratio (**c**:**d**) also decreased to 2:1 as the yield of the *syn*-THF increased



Scheme 2. General scheme for the synthesis of 1,2,4-triols.



2 R^1 = H
3 R^1 = C_3H_5 (ω-propenyl)
4 R^1 = $C_{11}H_{21}$ (ω-undecenyl)
5 R^1 = $C_{13}H_{25}$ (ω-tridecenyl)
6 R^1 = Ph
7 R^1 = *t*-Bu

8 R^1 = R^2 = CH_3
9 R^1 = R^2 = Ph
10 R^1 = R^2 = $(CH_2)_4$
11 R^1 = R^2 = $(CH_2)_5$
12 R^1 = R^2 = $(CH_2)_{11}$

13 R^1 = Ph

Figure 2. The 1,2,4-triols used in this study.

Table 1
Cyclodehydration or sulfonylation of 1,2,4-triols derived from aldehydes

1,2,4-triol — *anti*-THF (**c**) — *syn*-THF (**d**) — *anti*-2,4 diol tosylate (**e**)

Entry	Triol	R^1	Δ*A*-Value (kcal·mol^{-1})	Yield (%)		
				c	**d**	**e**
1	**2**	H	0		98[a]	0
2	**3a**	C_3H_5 (ω-propenyl)	1.68	82	0	0
3	**3b**	C_3H_5 (ω-propenyl)		0	12	66
4	**4a**	$C_{11}H_{21}$ (ω-undecenyl)	1.79	90	0	0
5	**4b**	$C_{11}H_{21}$ (ω-undecenyl)		0	12	74
6	**5a**	$C_{13}H_{25}$ (ω-tridecenyl)	1.79	85	0	0
7	**5b**	$C_{13}H_{25}$ (ω-tridecenyl)		0	12	75
8	**6a**	Ph	2.8	84	0	0
9	**6b**	Ph		0	9	83
10	**7a**	*t*-Bu	4.79	80	0	0
11	**7b**	*t*-Bu		0	0	87

[a] Isolated as the benzoate ester.

Table 2
Cyclodehydration or sulfonylation of 1,2,4-triols derived from ketones

1,2,4-triol — *anti*-THF (**c**) — *syn*-THF (**d**) — *anti*-2,4 diol tosylate (**e**)

Entry	Triol	R^1	R^2	Δ*A*-Value (kcal·mol^{-1})	Yield (%)		
					c	**d**	**e**
1	**8**	CH_3	CH_3	0		78	0
2	**9**	Ph	Ph	0		79	0
3	**10**	Cyclopentanone		0		72	14
4	**11**	Cyclohexanone		0		79	13
5	**12**	Cyclododecane		0		75	0
6	**13a**	Ph	CH_3	1.06	79	0	0
7	**13b**	Ph	CH_3	1.06	0	35	62

dramatically to 35% (Table 2, entries 6 and 7). The rationale for this diastereoselectivity is depicted in Figure 3, where the proposed transition state for cyclodehydration would presumably occur via the conformational isomer **IIb**, which clearly shows the improbability of the cyclization product (disfavoured), thus the C1 tosylate persists as the major product.

However, the results for compounds **8** and **9** (Table 2, entries 1 and 2), where the groups at C4 are identical (CH_3 or Ph, respectively), were surprising in that the THF (only one possible diastereomer **c** for the symmetrical ketones **8**–**12**) was formed as the exclusive product, in very good yields (>75%). Since there is only one possible conformational transition state, we expected that there would be a

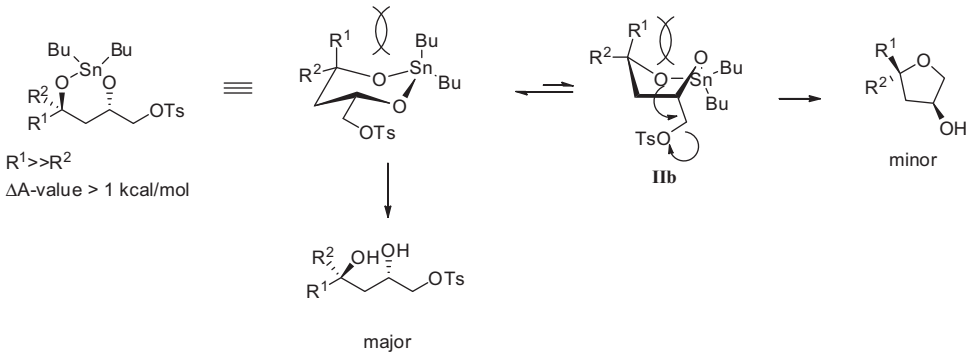


Figure 3. A proposed barrier to cyclodehydration for the *anti*-1,2,4-triols.

barrier to cyclodehydration from the axially positioned group, therefore a significant amount of tosylate should form. The exclusive formation of the THF suggests that this cyclization might arise as a consequence of a *gem*-disubstituent (Thorpe–Ingold) effect being the dominant driving force versus the tin chelation effect.[14] The reactions of 1,2,4-triols formed from simple cyclic ketones (Table 2, entries 3–5) fit this trend favouring the formation of spirocyclic 3-hydroxytetrahydrofurans in good yields (72–79%). However, the formation of minor monosulfonylated products (<15%) for the smaller cyclic ketones **10** and **11** (Table 2, entries 3 and 4) suggests that conformational rigidity may contribute to a slight barrier to cyclization, thereby increasing the 'tin chelation effect'.

We were pleasantly surprised to observe that the CDS protocol proved to be an improvement on the efficiency of previously reported methods for the synthesis of spirocyclic 3-hydroxytetrahydrofurans derived from cyclic ketones.[2b,5b,12c,15] For example, via the CDS method, the 3-hydroxytetrahydrofuran **12c** was formed in 79% yield, compared to the 33% yield (after 4 days) reported by Vasconcelos et al.[15a] Given the mild reaction conditions of our protocol, this method could represent a more favourable option for the synthesis of spirocyclic 3-hydroxytetrahydrofurans.

In summary, we have described further evidence that the tin-mediated cyclodehydration or sulfonylation of 1,2,4-triols is predictably diastereoselective and superior to previous observations where the observed diastereoselectivity has generally been poor.[16] Therefore, this protocol might find application in establishing the relative configuration of 1,2,4-triols by observing the formation/non-formation of sulfonylated products. This would be a valuable addition to the existing circular dichroic (CD) methods.[17] Finally, this method has the potential to be employed as a mild alternative for the stereoselective synthesis of substituted tetrahydrofurans from ketones and aldehydes, via 1,2,4-triols.

Acknowledgments

We acknowledge the institutional and financial support of the Tshwane University of Technology (TUT) and the financial support from the National Research Foundation (NRF-South Africa) for a Human and Institutional Capacity Development Programmes grant (GUN 62464) to C.M.N.; M.P.G. was supported by a grant-holder linked NRF student bursary for this study. We are grateful to the Department of Higher Education and Training (DHET-RSA) for an institutional grant for the purchase of a 400 MHz NMR spectrometer via the Infrastructure for Efficiency Funding (IEF).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.083.

References and notes

1. Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.
2. (a) Denney, D. B.; Denney, D. Z.; Gigantino, J. J. *J. Org. Chem.* **1984**, *49*, 2831–2832; (b) Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 7681–7685; (c) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Kishibata, N.; Izawa, K. *Org. Biomol. Chem.* **2004**, *2*, 2061–2070; (d) Yamaguchi, A.; Hiyoshi, N.; Sato, O.; Bando, K. K.; Shirai, M. *Green Chem.* **2009**, *11*, 48–52; (e) Tandon, V. K.; Van Leusen, A. M.; Wynberg, H. *J. Org. Chem.* **1983**, *48*, 2767–2769; (f) Hu, X.; Shan, Z.; Peng, X.; Li, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 2474–2478; (g) Pavlik, C.; Onorato, A.; Castro, S.; Morton, M.; Peczuh, M.; Smith, M. B. *Org. Lett.* **2009**, *11*, 3722–3725.
3. (a) Ramachandran, P. V.; Nair, H. N. G.; Gagare, P. D. *J. Org. Chem.* **2012**, *77*, 5394–5398; (b) Minuti, L.; Barattucci, A.; Bonaccorsi, P. M.; Di Gioia, M. L.; Leggio, A.; Siciliano, C.; Temperini, A. *Org. Lett.* **2013**, *15*, 3906–3909; (c) Chirskaya, M. V.; Vasil'ev, A. A.; Sergovskaya, N. L.; Shorshnev, S. V.; Sviridov, S. I. *Tetrahedron Lett.* **2004**, *45*, 8811–8813; (d) Yuasa, Y.; Tsuruta, H. *Liebigs Ann.* **1997**, 1877–1879; (e) van den Berg, R. J. B. H. N.; Boltje, T. J.; Verhagen, C. P.; Litjens, R. E. J. N.; van der Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2005**, *71*, 836–839.
4. (a) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Terlizzi, R.; Temperini, A.; Marini, F.; Santi, C.; Scarponi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1949–1955; (b) Lin, C.-W.; Liu, S.-W.; Hou, D.-R. *Org. Biomol. Chem.* **2013**, *11*, 5292–5299; (c) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003; (d) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717–1720; (e) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600–13601; (f) Mukai, C.; Sugimoto, Y.-I.; Ikeda, Y.; Hanaoka, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1161–1162; (g) Andrey, O.; Ducry, L.; Landais, Y.; Planchenault, D.; Weber, V. R. *Tetrahedron* **1997**, *53*, 4339–4352; (h) Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495–1498.
5. (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964; (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825; (c) Tamaru, Y.; Kawamura, S.-I.; Yoshida, Z.-I. *Tetrahedron Lett.* **1985**, *26*, 2885–2888; (d) Pulido, F. J.; Barbero, A.; Val, P.; Diez, A.; González-Ortega, A. *Eur. J. Org. Chem.* **2012**, *2012*, 5350–5356; (e) Andrey, O.; Glanzmann, C. C.; Landais, Y.; Parra-Rapado, L. *Tetrahedron* **1997**, *53*, 2835–2854; (f) Okimoto, Y.; Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 10223–10227; (g) Fujioka, H.; Maehata, R.; Wakamatsu, S.; Nakahara, K.; Hayashi, T.; Oki, T. *Org. Lett.* **2012**, *14*, 1054–1057; (h) Murakami, M.; Oike, H.; Sugawara, M.; Suginome, M.; Ito, Y. *Tetrahedron* **1993**, *49*, 3933–3946.
6. Brovetto, M.; Seoane, G. *J. Org. Chem.* **2008**, *73*, 5776–5785.
7. (a) Hartman, F. C.; Barker, R. *J. Org. Chem.* **1964**, *29*, 873–877; (b) Zheng, X.; Nair, V. *Tetrahedron* **1999**, *55*, 11803–11818; (c) Passiniemi, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2008**, *49*, 980–983.
8. Gamedze, M. P.; Maseko, R. B.; Chigondo, F.; Nkambule, C. M. *Tetrahedron Lett.* **2012**, *53*, 5929–5932.
9. Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4062–4072.
10. Roy, R.; Rey, A. W.; Charron, M.; Molino, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1308–1310.
11. (a) Clark, T. B.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 4109–4112; (b) Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86–89; (c) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem. Eur. J.* **2007**, *13*, 689–701; (d) Theurer, M.; Fischer, P.; Baro, A.; Nguyen, G. S.; Kourist, R.; Bornscheuer, U.; Laschat, S. *Tetrahedron* **2010**, *66*, 3814–3823; (e) Murakami, M.; Andersson, P. G.; Suginome, M.; Ito, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3987–3988; (f) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481–3484; (g) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168; (h) Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, *5*, 4231–4234; (i) George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 8544–8546.
12. (a) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087–3091; (b) Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1995**, *36*, 4885–4888; (c)

Moskalenko, A.; Belopukhov, S.; Ivlev, A.; Boev, V. *Russ. J. Org. Chem.* **2011**, *47*, 1091–1096; (d) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910–912.

13. *General method for cyclodehydration or sulfonylation (CDS):* To a 50 mL two-neck round-bottom flask equipped with a condenser were added the triol (0.175 mmol), *p*-TsCl (0.192 mmol), Bu_2SnO (0.0087 mmol) and Et_3N (0.192 mmol), and the mixture was heated to a gentle reflux in CH_2Cl_2 (2 mL, 0.1 M) for 3.5 h. The reaction was monitored by TLC. On completion, the reaction was quenched with satd NH_4Cl or MeOH (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with H_2O (15 mL) and brine (15 mL) before drying over $MgSO_4$. The solvent was evaporated and the crude residue was purified by column chromatography.
14. Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
15. (a) Vasconcelos, R. S.; Silva, L. F.; Giannis, A. *J. Org. Chem.* **2011**, *76*, 1499–1502; (b) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962–2964; (c) Chirskaya, M.; Vasil'ev, A.; Shorshnev, S.; Sviridov, S. *Russ. Chem. Bull.* **2006**, *55*, 1300–1303.
16. (a) Zhang, G.; Gong, X.; Yang, S.; Sun, B.; Liu, Y.; Tian, H. *Flavour Fragrance J.* **2014**, *29*, 349–354; (b) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496–2500.
17. (a) Zhao, N.; Zhou, P.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 636–651; (b) Rele, D.; Zhao, N.; Koji, N.; Nina, B. *Tetrahedron* **1996**, *52*, 2759–2776; (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087–9090.