Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6275–6280

Efficient one-pot *trans*-dihydroxylation of 2*H*-pyrans using dimethyldioxirane (DMD): synthesis of *trans*-3,4-dihydroxy-3,4-dihydro-*O*-methyloctandreolones, orixalone D, and *trans*-3,4-dihydroxy-3,4-dihydromollugin natural products

Xue Wang and Yong Rok Lee*

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Republic of Korea

Received 19 June 2007; accepted 5 July 2007
Available online 30 July 2007

Abstract—An efficient one-pot formation of *trans*-diols on 2*H*-pyranyl rings was achieved by dimethyldioxirane in wet acetone. This new methodology was applied to the synthesis of natural products containing *trans*-diol on the pyranyl rings such as *trans*-3,4-dihydroxy-3,4-dihydro-*O*-methyloctandreolones, orixalone D, and *trans*-3,4-dihydroxy-3,4-dihydromollugin.

1. Introduction

Molecules with a *cis*-(**1**–**7**) or *trans*-dihydroxyl group (**8**–**14**) on their 2*H*-pyranyl rings are distributed widely in nature (Fig. 1).[1] These compounds have a variety of interesting biological activities and potential medical applications.[2] This range of important biological activities and properties has stimulated research into the synthesis of molecules with *cis*- or *trans*-dihydroxy groups on the 2*H*-pyranyl ring. In particular, the development of a series of benzopyran-based potassium channel activators has generated considerable interest in the synthesis of *trans*-diols on the 2*H*-pyranyl rings.[3]

We recently reported that $Yb(OTf)_3$ or ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyl compounds or resorcinol with α,β-unsaturated aldehydes provide a rapid route to 2*H*-pyrans or benzopyrans.[4] These reactions involve the formal [3+3] cycloaddition for constructing 2*H*-pyran rings. The synthesized

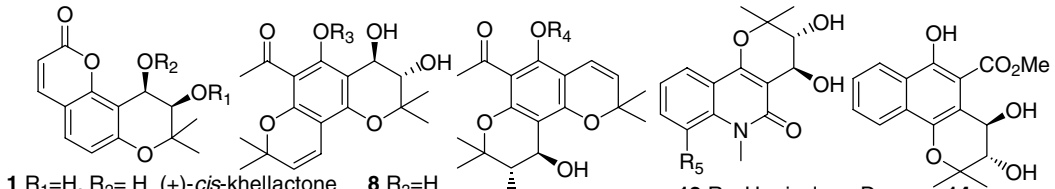


Figure 1. Naturally occurring molecules with *cis*- and *trans*-diol on the pyranyl rings.

Keywords: *trans*-Dihydroxylation; Dimethyldioxirane; *trans*-3,4-Dihydroxy-3,4-dihydro-*O*-methyloctandreolones; Orixalone D; *trans*-3,4-Dihydroxy-3,4-dihydromollugin.
* Corresponding author. Tel.: +82 53 810 2529; fax: +82 53 810 1496; e-mail: yrlee@yu.ac.kr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.022

2*H*-pyrans or benzopyrans appear ideal for making natural products or biologically active materials with *cis*- or *trans*-diols on the pyranyl rings. This Letter reports an efficient and convenient one-pot synthesis of *trans*-diols on the pyranyl rings using dimethyldioxirane. As an application of this methodology, we report the synthesis of biologically interesting natural products as racemates, *trans*-3‴,4‴-dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**),[5] *trans*-3″,4″-dihydroxy-3″,4″-dihydro-*O*-methyloctandreolone orixalone D (**11**),[6] and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**14**).[7]

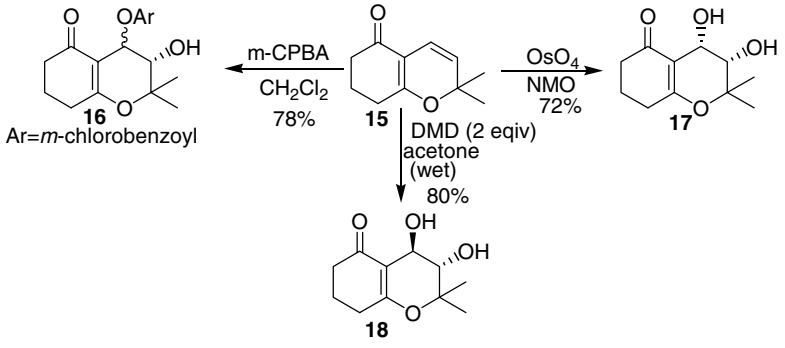
2. Results and discussion

The dihydroxylation of alkenes represents a unique synthetic method for generating 1,2-diols with a defined relative configuration.[8] A number of synthetic approaches for *cis*- and *trans*-dihydroxylation have been reported.[9–13] The most common protocol of *cis*-dihydroxylation is the use of OsO_4, $KMnO_4$, and RuO_4,[9] whereas that of *trans*-dihydroxylation is achieved by the treatment with a suitable peroxycarboxylic acid in a two-step reaction.[10] The reactions first produce an epoxide (oxirane), which then undergoes ring opening through the anti-attack of the corresponding nucleophiles to give *trans*-diols. However, in many cases, monoesters with a hydroxy group due to ring opening of the corresponding carboxylic acid are normally present in the reaction medium and are produced as a mixture of cis and trans-isomers.[10] The hydrolysis of this monoester provides the 1,2-diols as a mixture of cis and trans-isomers. In an attempt to prevent this, hydrogen peroxide and WO_3, SeO_2, V_2O_3, $VO(acac)_2$, and $MeReO_3$ as catalysts have been used as new oxidants to give the trans-diols.[11] An example of this is the reaction using $MMPP/H_2O_2$, which provides mainly *trans*-diols as a 9:1 mixture.[12] Furthermore, Sudalai also developed a 'transition-metal free' procedure for *trans*-dihydroxylation using $PhI(OAc)_2$/LiBr in a two-step reaction.[13] Only one example of dihydroxylation of hydroquinones using dimethyldioxirane is found in the literature.[14] However, in these reactions, 2,3-dihydroxycyclohexene-1,4-diones were obtained as a mixture of cis/trans-isomers along with quinones. In particular, there does not appear to be any efficient and general method for preparing *trans*-diols on the pyranyl rings as a one-pot procedure using dimethyldioxirane.

2*H*-Pyrans **15** and **19**–**28** are easily prepared by the ethylenediamine diacetate-catalyzed condensation of the corresponding 1,3-dicarbonyl compounds with 3-methyl-2-butenal according to a synthetic method reported by our group.[4] The reaction of compound **15** was first investigated using several oxidants (Scheme 1). The epoxidation of compound **15** using mCPBA at room temperature for 10 h in methylene chloride gave the hydroxyester **16** in 78% yield as a 1:1 mixture of cis and trans-isomers. Catalytic osmium tetroxide oxidation using 2 equiv of NMO in *t*-BuOH/THF/H_2O (10:3:1) at room temperature for 24 h gave the *cis*-diol **17** in 72% yield.[15] Interestingly, the treatment of compound **15** with 2 equiv of DMD in wet acetone at room temperature for 3 h provided the *trans*-diol **18** in 80% yield without any of the *cis*-diol **17**.[16] The stereochemical assignment of cis and trans products was easily defined by the observation of the coupling constants between the vicinal protons, H3–H4. The *J* value for this H3–H4 vicinal coupling in the cis-isomer **17** is 4.5 Hz, whereas it is 7.7 Hz for the trans-isomer **18**.[17]

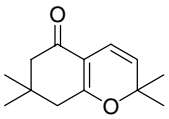
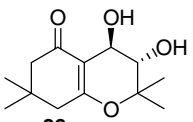
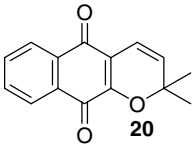
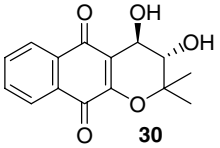
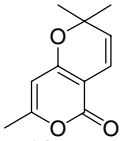
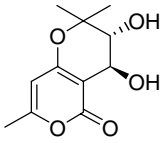
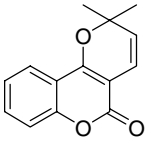
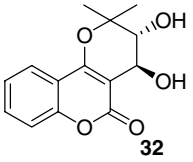
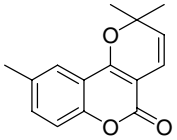
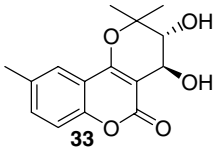
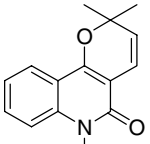
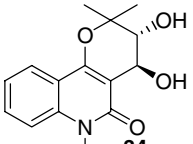
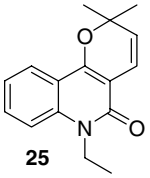
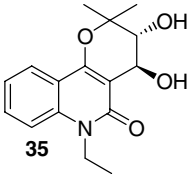
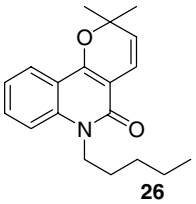
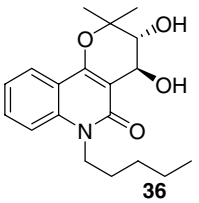
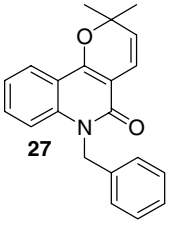
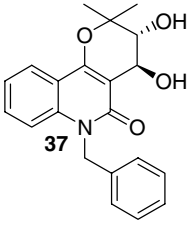
In order to extend the utility of this methodology, further reactions of a variety of compounds containing 2*H*-pyranyl rings were investigated. The results are shown in Table 1. A reaction between compound **19** and DMD in wet acetone at room temperature for 3 h gave compound **29** in 83% yield (entry 1). The treatment of biologically active dehydro-α-lapachone (**20**), isolated from *Zeyhera tuberculosa*,[18] with DMD at room temperature for 3 h afforded compound **30** in 78% yield (entry 2). Similarly, a reaction with compound **21** at room temperature for 3 h gave product **31** in 63% yield (entry 3). In the cases of biologically interesting pyranocoumarins **22**–**23** and pyranoquinolinones **24**–**27**, the expected products **32**–**37** were produced in 66–90% yields (entries 4-9). In the case of precocene I (**28**), product **38** was obtained in 61% yield (entry 10). These reactions provide a rapid route for the synthesis of *trans*-diols on the 2*H*-pyranyl rings.

An attempt was made to synthesize the naturally occurring materials, *trans*-3‴,4‴-dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**), *trans*-3″,4″-dihydroxy-3″,4″-dihydro-*O*-methyloctandreolone (**11**), orixalone D (**12**), and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**14**) as racemates using this methodology. *trans*-3‴,4‴-Dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**) are



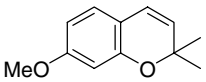
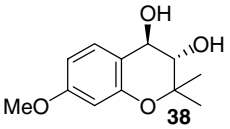
Scheme 1.

Table 1. Reactions of a variety of 2*H*-pyrans with DMD to give *trans*-diols

Entry[a]	Starting material	Time (h)	Product	Yield[b] (%)
1	 **19**	3	 **29**	83
2	 **20**	3	 **30**	78
3	 **21**	3	 **31**	63
4	 **22**	3	 **32**	90
5	 **23**	3	 **33**	71
6	 **24**	2	 **34**	66
7	 **25**	2	 **35**	81
8	 **26**	2	 **36**	72
9	 **27**	2	 **37**	76

(*continued on next page*)

Table 1 (*continued*)

Entry[a]	Starting material	Time (h)	Product	Yield[b] (%)
10	 **28**	3	 **38**	61

[a] 2 equiv of DMD was used in wet acetone.
[b] Only *trans*-diols were isolated.

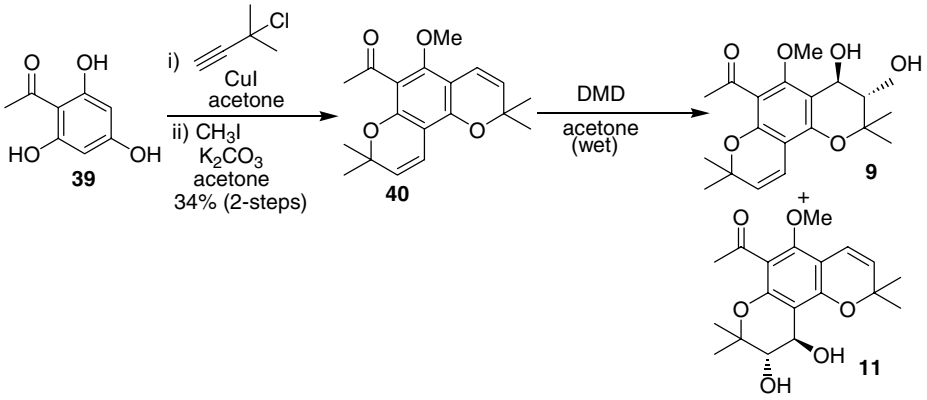
isolated primarily from the roots of *Melicope erromangensis*.[5] Orixalone D (**12**) is isolated from *Orixa japonica* (Rutaceae), and is considered to be one of the constituents of the crude drug 'Johzan'.[6] The leaves of this plant are used in Japan as an insecticide for livestock.[19] In China and other Asian countries, the root of this plant has been used in traditional medicine as febrifuges and analgesics.[20] Orixalone D derivatives were also found to inhibit the production of nitric oxide in murine macrophage-like RAW 264.7 cells stimulated with interferon-γ and lipopolysaccharide.[6] *trans*-3,4-Dihydroxy-3,4-dihydromollugin (**14**) was isolated from *Pentas longiflora*, which is an important medicinal plant in Tropical East Africa.[7] In Kenya, it is known as 'Nekilango' or 'Segimbe', and the roots of this plant are widely used as traditional medicines for treating tapeworm, itchy rashes, and pimples.[21] A decoction of the roots is also used as a cure for malaria. In Rwanda, this plant is known as 'Isagara', and the powder of the roots is used as an ointment to cure scabies and the skin disease, pityriasis versicolor.[22]

As shown in Scheme 2, compound **39**, which was used for the synthesis of the natural product **9**, was prepared using a known method.[23] The condensation of 2,4,6-trihydroxyacetophenone (**39**) with 3-chloro-3-methyl-1-butyne in the presence of copper(I) iodide followed by methylation of the phenol group with methyl iodide in acetone gave **40** in 34% overall yield (two steps).[23] A reaction of compound **40** with 1.1 equiv of DMD in wet acetone at room temperature for 3 h afforded compound **9** in 53% yield, whereas that with 2 equiv of DMD at room temperature gave compounds **9** and **11** in 52% and 27% yields, respectively. The structures of the synthetic materials **9** and **11** were clearly assigned by a comparison with the reported ^{1}H NMR data in the literature for the natural products.[5]

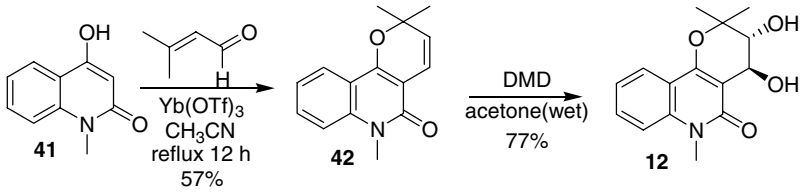
Compound **42**, which was used for the synthesis of the orixalone D (**12**), was prepared using commercially available compound **41** in 57% yield in a one-step reaction using an earlier reported method (Scheme 3).[4a] The treatment of compound **42** with 2 equiv of DMD in wet acetone gave compound **12** in 77% yield. The spectroscopic data of the synthetic material **12** was same as the data reported in the literature for the natural product.[6]

The synthesis of the natural product **14** was accomplished from mollugin (**45**), which is also a natural product. Mollugin (**45**) was synthesized in three-steps starting from compound **43** using the known procedure (Scheme 4).[24] The esterification of compound **43** with diazomethane followed by condensation with 2-methyl-3-buten-2-ol in the presence of boron trifluoride diethyl etherate gave compound **44** in 46% overall yield (two steps). The oxidation of compound **44** with DDQ in refluxing toluene afforded natural compound **45** in 56% yield. The treatment of compound **45** with 2 equiv of DMD at room temperature for 3 h afforded compound **14** in 62% yield. The spectral data of the synthetic material **14** were identical with that described in the literature.[25]

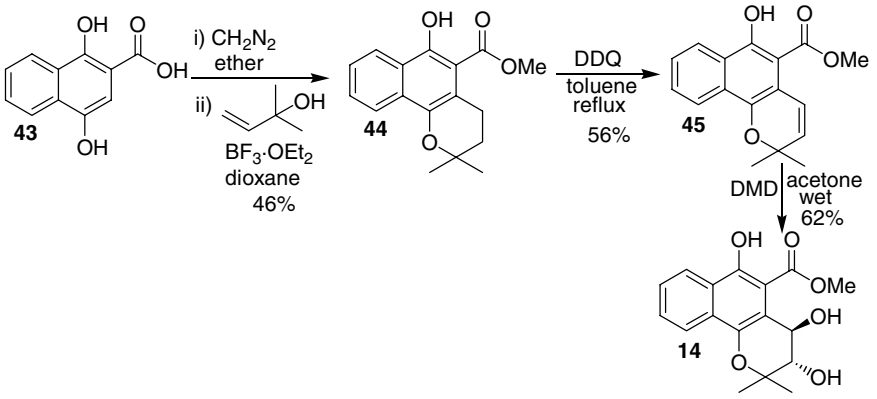
In conclusion, a new and general procedure for the synthesis of *trans*-diols on the 2*H*-pyranyl rings was developed using DMD in wet acetone. This new methodology was applied to the synthesis of naturally occurring



Scheme 2.



Scheme 3.



Scheme 4.

trans-3‴,4‴-dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**), *trans*-3″,4″-dihydroxy-3″,4″-dihydro-*O*-methyloctandreolone (**11**), orixalone D (**12**), and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**14**).

Acknowledgment

This research was supported by the Yeungnam University research Grants in 207-A-235-032.

References and notes

1. (a) Valencia-Islas, N.; Abbas, H.; Bye, R.; Toscano, R.; Mata, R. *J. Nat. Prod.* **2002**, *65*, 828; (b) Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pusset, J.; Chauviere, G. *J. Nat. Prod.* **1985**, *48*, 772.
2. (a) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1999**, *42*, 2662; (b) Ishikawa, T. *Heterocycles* **2000**, *53*, 453; (c) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664.
3. (a) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194; (b) Buckle, D. R.; Eggleston, D. S.; Pinto, I. L.; Smityh, D. G.; Tedder, J. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1161; (c) Bergmann, R.; Eiermann, V.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 2759; (d) Atwal, K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russell, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971.
4. (a) Lee, Y. R.; Kweon, H. I.; Koh, W. S.; Min, K. R.; Kim, Y.; Lee, S. H. *Synthesis* **2001**, 1851; (b) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539; (c) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603; (d) Lee, Y. R.; Choi, J. H.; Trinh, D. T. L.; Kim, N. W. *Synthesis* **2005**, 3026; (e) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853.
5. Muyard, F.; Bissoue, A. N.; Bevalot, F.; Tillequin, F.; Cabalion, P.; Vaquette, J. *Phytochemistry* **1996**, *42*, 1175.
6. Ito, C.; Itoigawa, M.; Furukawa, A.; Hirano, T.; Murata, T.; Kaneda, N.; Hisada, Y.; Okuda, K.; Furukawa, H. *J. Nat. Prod.* **2004**, *67*, 1800.
7. El-Hady, S.; Bukuru, J.; Kesteleyn, B.; Puyvelde, L. V.; Van, T. N.; De Kimpe, N. *J. Nat. Prod.* **2002**, *65*, 1377.
8. (a) Haines, A. H. In *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 437; (b) Curei, R. In *Advanced in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, Chapter 1; (c) Adam, W.; Hadjiarapoglou, L. P.; Curei, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; p 195; (d) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187; (e) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205; (f) Curei, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.
9. (a) Schroder, M. *Chem. Rev.* **1980**, *80*, 187; (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263; (c) Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402; (d) Ogino, T. *Tetrahedron Lett.* **1980**, *21*, 177; (e) Weber, W. P.; Shepherd, J. P. *Tetrahedron Lett.* **1972**, *13*, 4907; (f) Ho, C. M.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3303; (g) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402; (h) Ogino, T.; Mochizuki, K. *Chem. Lett.* **1979**, 4.
10. (a) Plesnicar, B. In *Oxidations in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; p 211, Part C; (b) Baragliu, A.; Grandolini, G.; Rossi, C.; Casinovi, C. G. *Tetrahedron* **1980**, *36*, 645; (c) Bachhawat, J. M.; Mathur, N. K. *Tetrahedron Lett.* **1971**, *12*, 691.
11. (a) Xie, G.; Xu, L.; Hu, S.; Ma, S.; Hou, W.; Tao, F. *Tetrahedron Lett.* **1988**, *29*, 2967; (b) Payne, G. B.; Smith, C. W. *J. Org. Chem.* **1957**, *22*, 1682; (c) Treibs, W.; Leichsenring, G.; Roder, H. *Chem. Ber.* **1953**, *86*, 616; (d) Éll, A. H.; Jonsson, S. Y.; Börje, A.; Adolfsson, H.;

Bäckvall, J.-E. *Tetrahedron Lett.* **2001**, *42*, 2569; (e) Cristea, I.; Kozma, E.; Batiu, C. *Tetrahedron: Asymmetry* **2002**, *13*, 915.
12. Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141.
13. Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.
14. Adam, W.; Schonberger, A. *Tetrahedron Lett.* **1992**, *33*, 53.
15. Gremyachinskiy, D.; Samoshin, V. V.; Gross, P. H. *Tetrahedron Lett.* **2003**, *44*, 6587.
16. Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
17. Spectral data for *cis*-diol **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (1H, d, $J = 4.5$ Hz), 4.04 (2H, br s), 3.61 (1H, d, $J = 4.5$ Hz), 2.40–2.27 (4H, m), 1.95–1.86 (2H, m), 1.40 (3H, s), 1.17 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 172.6, 109.8, 80.9, 70.4, 62.8, 37.1, 29.1, 24.1, 23.9, 20.9; IR (neat) 3485, 3402, 2953, 2890, 1601, 1435, 1370, 1269, 1192, 1109, 1011, 930, 901, 822 cm^{-1}; MS(EI) 212 (M^+), 195, 179, 142, 141, 139, 95, 84, 72, 57, 55. *trans*-Diol **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (1H, d, $J = 7.7$ Hz), 3.88 (2H, br s), 3.57 (1H, d, $J = 7.7$ Hz), 2.38–2.29 (4H, m), 1.97–1.89 (2H, m), 1.42 (3H, s), 1.16 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.7, 111.9, 81.7, 75.1, 67.5, 36.9, 28.9, 26.3, 20.9, 19.7; IR (neat) 3500, 2950, 1605, 1381, 1265, 1186, 1125, 1053, 929, 820 cm^{-1}; MS(EI) 212 (M^+), 194, 179, 142, 141, 139, 112, 95, 84, 78, 72, 63, 57, 55.
18. Duarte Weinberg, M. D. L.; Gottlieb, O. R.; De Oliveira, G. G. *Phytochemistry* **1976**, *15*, 570.
19. *Newly Revised Illustrated Medicinal Plants of the World*; Hokuryukan Co., Ltd: Tokyo, 2002; p 250.
20. *Chinese Material Medica Dictionary*; Jiangsu New Medical College, Ed.; Shanghai Science & Technology Press: Shanghai, 1977; Vol. 2, p 1888.
21. Kokwaro, J. O. *Medicinal Plants of East Africa*; East African Literature Bureau: Kampala, Nairobi, Dar es Salaam, 1976; p 190.
22. (a) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelius, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329; (b) Van Puyvelde, L.; Geyen, D.; Ayobangira, F.-X.; Hakizamungu, E.; Nshimiyimana, A.; Kalisa, A. *J. Ethnopharmacol.* **1985**, *13*, 209.
23. Pernin, R.; Muyard, F.; Bévalot, F.; Tillequin, F.; Vaquette, J. *J. Nat. Prod.* **2000**, *63*, 245.
24. Ho, L.-K.; Yu, H.-J.; Ho, C.-T.; Don, M.-J. *J. Chin. Chem.* **2001**, *48*, 77.
25. Itokawa, H.; Ibrahim, Z.; Qiao, Y.-F.; Takeya, K. *Chem. Pharm. Bull.* **1993**, *41*, 1869.