Tetrahedron Letters 55 (2014) 2266–2269

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of the tetrahydrofuran unit of varitriol and γ-butyrolactones from 5-oxabicyclo[2.1.1]hexane derivative via oxidative cleavage reactions

Surendra H. Mahadevegowda [b], Faiz Ahmed Khan [a,*]

[a] Department of Chemistry, Indian Institute of Technology Hyderabad, Ordnance Factory Estate, Yeddumailaram 502205, India
[b] Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India

ARTICLE INFO

Article history:
Received 7 January 2014
Revised 15 February 2014
Accepted 23 February 2014
Available online 2 March 2014

Keywords:
Antitumor natural product
Deacetoxylation
Pyridinium dichromate
Bis-oxidative cleavage

ABSTRACT

A formal synthesis of marine-derived antitumor natural product varitriol from a 5-oxabicyclo[2.1.1]hexane derivative is described. A tetrahydrofuran unit of varitriol embedded with four contiguous stereocenters was synthesized with an overall yield of 10.2% in 11 steps from an oxa-bicyclic system. An unprecedented oxidative cleavage reaction involving scissoring of two C—C bonds at oxa-quaternary carbon of THFs leading to γ-butyrolactones was reported and a plausible mechanism has been proposed.

Varitriol is a marine origin low molecular weight antitumor natural product, it was isolated by Barrero and co-workers in 2002.[1] The biological activity profile of varitriol was tested against cancer lines within the 60 cell line panel of NCI and found to be a potent cytotoxic toward renal ($GI_{50} = 1.63 \times 10^{-7}$ M), breast ($GI_{50} = 2.10 \times 10^{-7}$ M) and CNS ($GI_{50} = 2.44 \times 10^{-7}$ M) cancer cells.[1,2] The interesting structure due to contiguously substituted tetrahydrofuran connected with aromatic moiety and the potent anticancer activity toward human cancer cell lines attracted the attention of various synthetic groups. The total synthesis of (−)-varitriol and absolute configuration assignment were reported by Jennings and co-worker[3] in 2006 and then absolute configuration of (+)-varitriol (**1**) was established (Fig. 1).

The first total synthesis of **1** was reported by Shaw and coworker in 2008 starting from D-mannopyranoside and 2,6-dihydroxybenzoic acid.[4a] Furthermore, other reports have appeared in the literature for the total synthesis of (+)-varitriol by utilizing various sugar based chiral pool starting materials.[4b–g] Recently, a total synthesis involving Corey Chaykovsky reaction and triethylamine mediated epimerization as the key steps to construct the stereochemically pure furanoside unit of natural product has been reported.[4h] Additionally, carbohydrate based chiral pool synthetic routes employing transition metal catalyst in the bicyclization of

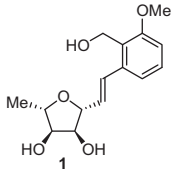


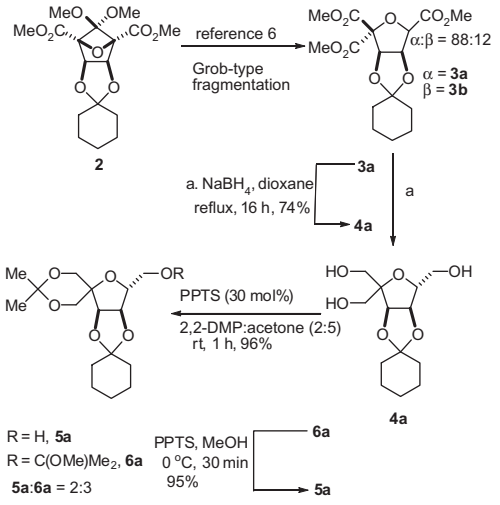
Figure 1. Structure of (+)-varitriol (**1**).

unsaturated polyol,[4i] vinyl oxirane ring expansion,[4j] α-hydroxyallene cycloisomerization[4k] reactions were also reported to achieve the synthesis of natural product. Likewise, in just appeared report, another total synthesis of **1** was disclosed using CSA induced intramolecular epoxide opening reaction to synthesize THF moiety of the natural product.[4l] The promising cytotoxicity of **1** also inspired some research groups toward synthesis of its analogues.[4g,k,m] Although, several reports are known for the synthesis of varitriol (**1**), we consider **1** as a target molecule in order to explore the in-house oxa-bridged derivatives[5] by using our recently reported methodology.[6]

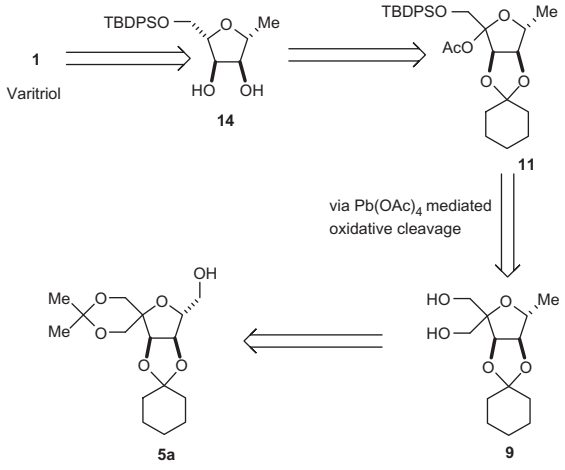
As a part of our research program on exploration of the chemistry of oxa-bridged derivatives,[7] very recently we reported an efficient Lewis acid mediated Grob-type fragmentation reaction of 5-oxabicyclo[2.1.1]hexane system to access 2,2,5-trisubstituted tetrahydrofuran building blocks.[6] Ready availability of these diastereomerically pure oxa-bridged compounds in gram-scale

* Corresponding author. Tel.: +91 40 23016084.
E-mail address: faiz@iith.ac.in (F.A. Khan).

http://dx.doi.org/10.1016/j.tetlet.2014.02.082
0040-4039/



Scheme 1. Synthesis of THF alcohol **5a** from 5-oxabicyclo[2.1.1]hexane **2**.



Scheme 2. Retrosynthetic plan for synthesis of varitriol (**1**) via $Pb(OAc)_4$ mediated oxidative cleavage of β-hydroxy ether.

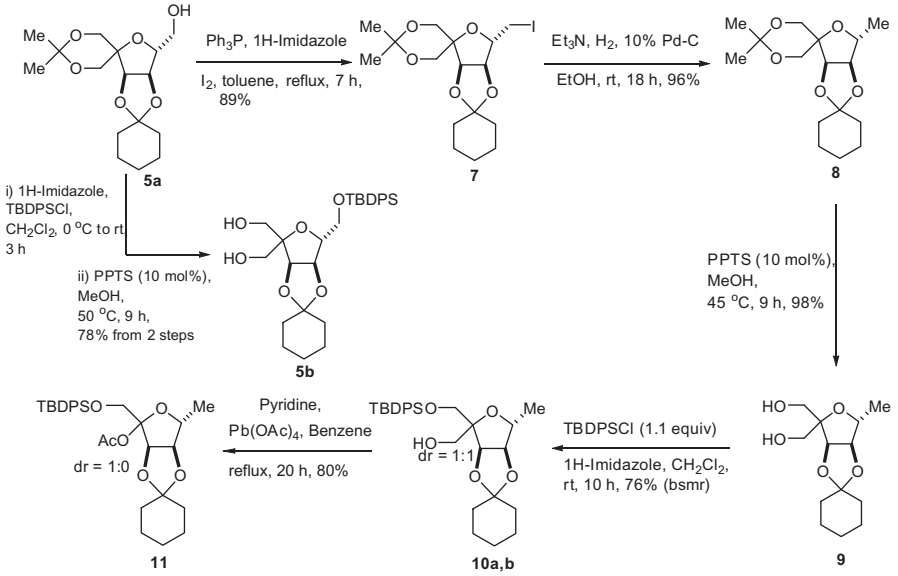
quantities prompted us to utilize them for the synthesis of biologically active natural products.

The oxygenated tetrahydrofuran tricarboxylates **3a**,**b** (dr = 88:12) could be prepared from oxa-bicycle **2** via $BF_3{\cdot}OEt_2$ mediated chemoselective Grob-type fragmentation reaction in excellent yield (97%). The chromatographically separable tetrahydrofuran derivative **3a** was converted into corresponding triol **4a** by reduction with $NaBH_4$ in refluxing 1,4-dioxane. When triol **4a** was subjected to acetonide protection with 2,2-DMP/acetone (2:5) using pyridinium *p*-toluenesulfonate (30 mol %), the desired monoalcohol **5a** and mixed acetal **6a** were obtained in 2:3 ratio with 96% yield. The mixed acetal was selectively deprotected by treating with PPTS (1.5 equiv) in MeOH at 0 °C to afford alcohol **5a** in 95% yield (Scheme 1).

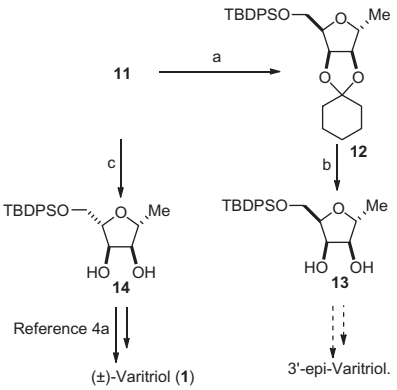
In 2010, Bourgeois and co-worker reported a diastereoselective synthesis of (±)-1′,4′-dimethyluridine by utilizing $Pb(OAc)_4$ mediated decarboxylation/O-glycosylation reaction to generate anomeric acetate of a tetrahydrofuran.[8a] Moreover, Alvarez-Manzaneda group reported lead(IV) acetate mediated cleavage of β-hydroxy ethers leading to α-acetoxy ethers.[8b] In our approach, we planned to synthesize furanoside portion of varitriol without oxidizing the hydroxymethyl group to carboxylic acid and employing $Pb(OAc)_4$ mediated oxidative cleavage. The schematic plan for the construction of the THF unit of varitriol via $Pb(OAc)_4$ mediated oxidative cleavage of β-hydroxy ether is outlined in Scheme 2.

The synthesis of acetoxylated THF **11** from diastereomerically pure alcohol (**5a**) is depicted in Scheme 3. The furanyl alcohol (**5a**) was converted into corresponding iodide **7** in 89% yield.[9] When furanyl iodide **7** was treated with Et_3N, 10% Pd–C in EtOH under hydrogen atmosphere, it delivered THF **8** in 96% yield. Chemoselective deprotection of acetonide **8** with PPTS (10 mol %) in MeOH afforded the diol **9** in 98% yield. Subsequently, the selective mono TBDPS ether protection was carried out on diastereotopic 1,3-diol to afford mono alcohols **10a**,**b** (dr = 1:1). The treatment of THF alcohols (**10a**,**b**) with lead(IV) acetate and 3.0 equivalents of pyridine in refluxing benzene elicited oxidative cleavage at oxa-quaternary center to afford acetoxy-tetrahydrofuran **11** (dr = 1:0) in 80% yield. Further, compound **5a** was transformed into 1,3-diol **5b** with an overall yield of 78% in 2 steps.

Having sufficient quantity of acetoxy-tetrahydrofuran **11** in hand, we focused our attention on the stereoselective reductive



Scheme 3. Synthesis of acetoxylated-tetrahydrofuran **11** from furanyl alcohol (**5a**).



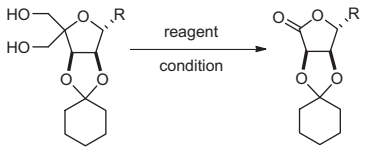
Scheme 4. Diastereoselective reductive deacetoxylation of compound **11** for the synthesis of THFs **13** and **14**. Reagents and conditions: (a) $BF_3{\cdot}OEt_2/Et_3SiH$, −10 °C, CH_2Cl_2, 50 min, 78%. (b) $AcOH/H_2O$ (4:1), 100 °C, 3 h, 42%. (c) (i) $AcOH/H_2O$ (4:1), 100 °C, 3 h. (ii) $BF_3{\cdot}OEt_2$, Et_3SiH, −30 °C, CH_2Cl_2, 1 h, 34% (from 2 steps).

deacetoxylation using $BF_3{\cdot}OEt_2/Et_3SiH$ as represented in Scheme 4. Initially, treatment of O-glycosylated tetrahydrofuran **11** with $BF_3{\cdot}OEt_2/Et_3SiH$ in CH_2Cl_2 at −10 °C afforded a diastereomerically pure 2,5-*trans*-disubstituted THF **12** in 78% yield. The relative stereochemistry of compound **12** was confirmed by 2D NMR (COSY and NOESY experiment). The cyclohexylidene deprotection of **12** in $AcOH/H_2O$ (4:1) at 100 °C gave diol **13** in 42% yield. Additional proof to corroborate the proposition that 2,5-*cis* compound was not obtained came from ^1H and ^{13}C NMR data of **13** which did not match with the literature reported values[4a,j] for the corresponding 2,5-*cis* THF. In view of the fact that the presence of a protecting group gave 2,5-*trans*-disustituted stereochemistry, we anticipated that initial deprotection of the cyclohexylidene group followed by reductive deacetoxylation might give desired 2,5-*cis*-disubstituted tetrahydrofuran derivative.[10] By this consideration, deprotection of the cyclohexylidene group of **11** was carried with $AcOH/H_2O$ (4:1) at 100 °C. After filtration of reaction mass through a short column of silica gel, the obtained residue was treated with $BF_3{\cdot}OEt_2/Et_3SiH$ in CH_2Cl_2 at −30 °C. Purification of the reaction mixture furnished the diol **14** in diastereomerically pure form in 34% overall yield (from **11**). The ^1H and ^{13}C NMR data of compound **14** were in close agreement with the two literature reports[4a,j] (for details see S38 in Supporting information).

Instances of side reactions such as C—C bond cleavage during Cr(VI)-mediated oxidation of alcohols are not uncommon in the literature.[11,12a,b] In some cases, the tertiary 1,2-diols could be converted to diones with concomitant C–C bond cleavage using PDC,[13a] and also depending on the reactivity of 1,4-[13b] and 1,5-diols,[13c] these could be transformed into γ- and δ-lactones respectively via hemi acetal formation followed by oxidation. Chandrasekaran and co-worker reported PCC-mediated oxidation of THF methanol derivatives to γ-butyrolactones.[13d] Additionally, Ryu and coworker observed the formation of lactonic nucleoside derivatives during PDC mediated oxidation of the 5′-hydroxymethyl group of nucleosides.[12a] During the last decade, efficient Cr(VI) catalyzed oxidative cleavage of tertiary alcohols of THPs and THFs was reported by Stark and coworker using periodic acid as an oxidant by the expulsion of acetone moiety.[13e] The oxidative cleavage of C—C bonds, which occur during the course of Cr(VI)-mediated oxidation are important not only from the mechanistic or catalytic point of view, but also play a role in creating new functionalities which are difficult to achieve by other methods even at high temperature[13f] or via deformylation[13g] or decarboxylation[13h] routes. Further, Cr(VI)-mediated selective cleavage of the β-hydroxymethyl group to furnish γ- and δ-lactones are utilized in the total synthesis of several natural products like (−)-*trans*-cembranolide,[14a] methyl-L-callipeltose,[14b] simplactone B,[14c] (−)-tetrahydrolipstatin,[14d] (+)-prelactones B, C, and V.[14e] Here we wish to report, an unexpectedly observed pyridinium dichromate/acetic anhydride promoted bis-oxidative cleavage reaction of hydroxymethyl groups at C2-position of THFs leading to γ-butyrolactones.

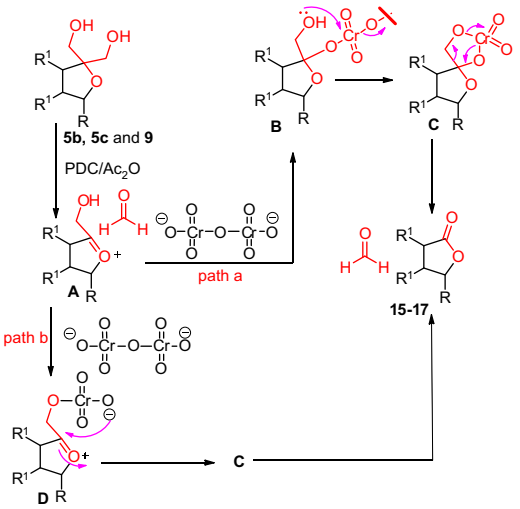
During Ru(III)-catalyzed oxidation[15] of bis-hydroxymethyl groups of **5b** to prepare corresponding geminal esters to employ Krapcho decarboxylation, we isolated γ-lactone **15** in 14% yield. The oxidation of oxa-quaternary carbon to lactone via cleavage of two carbon–carbon bonds is fairly interesting, and to improve the yield of reaction our attention was drawn to check the reactivity with other oxidizing agents. From the literature support,[12a] we decided to examine the efficiency of bis-oxidative cleavage of THFs using Cr(VI) reagents. The results of pyridinium dichromate (PDC) and PDC/Ac_2O mediated bis-oxidative cleavage reaction of THF alcohols (**5b**, **5c** and **9**) are depicted in Table 1. Among the conditions tested, the oxidative cleavage reaction with pyridinium dichromate alone in DMF is sluggish and afforded lactones in less yields (entry 2 and 4). Further, the pyridinium dichromate and

Table 1
A bis-oxidative cleavage reaction of THF alcohols (**5b**, **5c**, and **9**)



Entry[a]	Substrate, R	Reagent	Product, R	Time (h)	Yield[c] (%)
1[b]	**5b**, R = $CH_2OTBDPS$	$RuCl_3{\cdot}3H_2O$, $NaIO_4$	**15**, R = $CH_2OTBDPS$	2.5	14
2	**5b**, R = $CH_2OTBDPS$	PDC	**15**, R = $CH_2OTBDPS$	40	18
3	**5b**, R = $CH_2OTBDPS$	PDC/Ac_2O	**15**, R = $CH_2OTBDPS$	1	54
4	**5c**, R = CH_2OBn	PDC	**16a**, R = CH_2OBn	14	13
5[d]	**5c**, R = CH_2OBn	PDC/Ac_2O	**16a**, R = CH_2OBn **16b**, R = CH_2OBz **16a**:**16b** = 7:4	1	55
6	**9**, R = Me	PDC/Ac_2O	**17**, R = Me	1	60

[a] All the reactions were carried out in anhydrous DMF solvent unless specified.
[b] The reaction was carried out in $CCl_4/CH_3CN/H_2O$ (1:1:1.5) solvent system.
[c] Isolated yield of product.
[d] The ratio of **16a** and **16b** was determined after debenzylation of inseparable products **16a**,**b**.



Scheme 5. A plausible mechanism of PDC/Ac_2O-mediated bis-oxidative cleavage reaction at oxa-quaternary carbon of THFs (**5b**, **5c** and **9**).

acetic anhydride combination furnished lactones[16] with moderate yields in shorter interval of time (entry 3, 5 and 6).

A detailed plausible mechanism[11] of pyridinium dichromate/acetic anhydride promoted bis-oxidative cleavage reaction of THF alcohols (**5b**, **5c**, and **9**) to afford lactones (**15**–**17**) is depicted in Scheme 5. Initially, the treatment of THFs with PDC/Ac_2O causes C_α—C_β bond scission, driven by the generation of an oxonium intermediate **A** with expulsion of a formaldehyde. Later, intermediate **A** could react with another equivalent of dichromate in two possible path ways (path a and path b) to form intermediates **B** and **D**. The alcohol **B** has been formed by the direct trapping of oxonium intermediate with dichromate. Whereas, **D** is resulted by the reaction of free hydroxyl group with dichromate. Subsequently, via path a, an intramolecular reaction of free hydroxyl with electrophilic chromium center of dichromate would deliver a five membered cyclic chromate ester intermediate **C**. On the other hand, via path b, the intermediate **C** could be formed by the intramolecular reaction of chromate and oxonium of **D**. Eventually, the reductive decomposition of cyclic chromate ester **C** through C_α—C_β bond cleavage delivers γ-lactones (**15**–**17**) with the liberation of another equivalent of formaldehyde in both path a and b.

In conclusion, we have reported a stereoselective strategy to access the tetrahydrofuran unit of (±)-varitriol. An oxa-bridged bicyclic compound is used as a new template for the formal synthesis of racemic varitriol via lead(IV) acetate mediated oxidative cleavage reaction. Furthermore, direct deacetoxylation of compound **11** afforded a diastereomerically pure 2,5-*trans*-disubstituted THF **12** which could serve as potential precursors for the synthesis of stereoisomers of varitriol. An oxidative cleavage of two hydroxymethyl groups at C2-position of THFs leading to γ-butyrolactones is reported. A plausible mechanism of bis-oxidative cleavage via five membered cyclic chromate ester has been discussed.

Acknowledgments

F.A.K. gratefully acknowledges CSIR for financial support. S.H.M. thanks CSIR, India for research fellowship.

Supplementary data

The detailed experimental procedures and spectroscopic data are available in supplementary material. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.082.

References and notes

1. Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364.
2. Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, *40*, 2676.
3. Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720.
4. (a) Kumar, V.; Shaw, A. K. *J. Org. Chem.* **2008**, *73*, 7526; (b) Ghosh, S.; Pradhan, T. K. *J. Org. Chem.* **2010**, *75*, 2107; (c) Srinivas, B.; Sridhar, R.; Rama Rao, K. *Tetrahedron* **2010**, *66*, 8527; (d) Karlubikova, O.; Palik, M.; Lasikova, A.; Kozisek, J.; Gracza, T. *Synthesis* **2010**, *20*, 3449; (e) Zeng, J.; Seenuvasan, V.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42; (f) Nagarapu, L.; Paparaju, V.; Satyender, A.; Rajashaker, B. *Tetrahedron Lett.* **2011**, *52*, 7075; (g) Ghosal, P.; Sharma, D.; Kumar, B.; Meena, S.; Sinha, S.; Shaw, A. K. *Org. Biomol. Chem.* **2011**, *9*, 7372; (h) Vamshikrishna, K.; Srihari, P. *Tetrahedron* **2012**, *68*, 1540; (i) Palik, M.; Karlubikova, O.; Lasikova, A.; Kozisek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, *5*, 709; (j) Brichacek, M.; Batory, L. A.; McGrath, N. A.; Njardarson, J. T. *Tetrahedron* **2010**, *66*, 4832; (k) Sun, T.; Deutsch, C.; Krause, N. *Org. Biomol. Chem.* **2012**, *10*, 5965; During our manuscript preparation this report was appeared: (l) Sudhakar, G.; Raghavaiah, J. *J. Org. Chem.* **2013**, *78*, 8840; (m) Senthilmurugan, A.; Aidhen, I. S. *Eur. J. Org. Chem.* **2010**, *3*, 555.
5. Khan, F. A.; Dash, J.; Sudheer, Ch.; Sahu, N.; Parasuraman, K. *J. Org. Chem.* **2005**, *70*, 7565. and references therein..
6. Mahadevegowda, S. H.; Khan, F. A. *Tetrahedron* **2013**, *69*, 8494.
7. For our previous applications of 5-oxabicyclo[2.1.1]hexane system see: (a) Khan, F. A.; Parasuraman, K. *Chem. Commun.* **2009**, 2399; (b) Khan, F. A.; Parasuraman, K.; Donnio, B. *Tetrahedron* **2010**, *66*, 8745.
8. (a) Sautrey, G.; Bourgeois, D.; Périgaud, C. *Org. Biomol. Chem.* **2010**, *8*, 378; (b) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Alvarez-Manzaneda, R.; Muñoz, P. E.; Jimenez, F.; Bouanou, H. *Tetrahedron* **2011**, *67*, 8910.
9. Perali, R. S.; Mandava, S.; Bandi, R. *Tetrahedron* **2011**, *67*, 4031.
10. Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 517.
11. Tojo, G.; Fernández, M. Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice. In *Basic Reactions in Organic Synthesis*; Tojo, G., Ed.; Springer: New York, 2006; pp 1–95.
12. (a) Kim, J. N.; Ryu, E. K. *Tetrahedron Lett.* **1992**, *33*, 3141; (b) Cossío, F. P.; López, M. C.; Palomo, C. *Tetrahedron* **1987**, *43*, 3963.
13. (a) Maki, S.; Ishihara, J.; Nakanishi, K. *J. Ind. Chem. Soc.* **2000**, *77*, 651; (b) Hariprakasha, H. K.; Subba Rao, G. S. R. *Ind. J. Chem.* **1998**, *37B*, 851; (c) Suzuki, T.; Ohmori, K.; Suzuki, K. *Org. Lett.* **2001**, *3*, 1741; (d) Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* **1990**, *31*, 2775; (e) Roth, S.; Stark, C. B. W. *Chem. Commun.* **2008**, 6411; (f) Modak, A.; Naveen, T.; Maiti, D. *Chem. Commun.* **2013**, 252; (g) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Liable-Sands, L. M.; Rheingold, A. L. *Organometallics* **1999**, *18*, 5311; (h) Dhavale, D. D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 4100.
14. (a) Taber, D. F.; Song, Y. *J. Org. Chem.* **1997**, *62*, 6603; (b) Huang, H.; Panek, J. S. *Org. Lett.* **1991**, *2003*, 5; (c) Reddy, M. S.; Narender, M.; Rao, K. R. *Tetrahedron* **2007**, *63*, 11011; (d) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995; (e) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133.
15. Parker, K. A.; Xie, Q. *Org. Lett.* **2008**, *10*, 1349.
16. The resulted γ-butyrolactones, (**15**, **16a,b** and **17**) after bis-oxidative cleavage of **5b**, **5c** and **9** are the derivatives of (±)-2,3-*O*-cyclohexylidene-ribonolactone and for the chemical synthesis of ribonolactone see: (a) Takano, S.; Inomata, K.; Ogasawara, K. *Heterocycles* **1988**, *27*, 2413; (b) Liu, D.; Caperelli, C. A. *Synthesis* **1991**, 933.