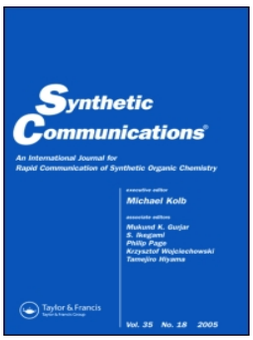


Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Efficient and highly selective cyclization induced by Lewis acid to generate 2-hydroxyl-α-cyclogeraniol

Zi Wang, Weiyi Qi, Yixuan Yan, Youhong Hu & Linhua Song

To cite this article: Zi Wang, Weiyi Qi, Yixuan Yan, Youhong Hu & Linhua Song (2016) Efficient and highly selective cyclization induced by Lewis acid to generate 2-hydroxyl-α-cyclogeraniol, Synthetic Communications, 46:23, 1932-1939, DOI: 10.1080/00397911.2016.1239739

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1239739

SYNTHETIC COMMUNICATIONS®
2016, VOL. 46, NO. 23, 1932–1939
http://dx.doi.org/10.1080/00397911.2016.1239739

Taylor & Francis
Taylor & Francis Group

Efficient and highly selective cyclization induced by Lewis acid to generate 2-hydroxyl-α-cyclogeraniol

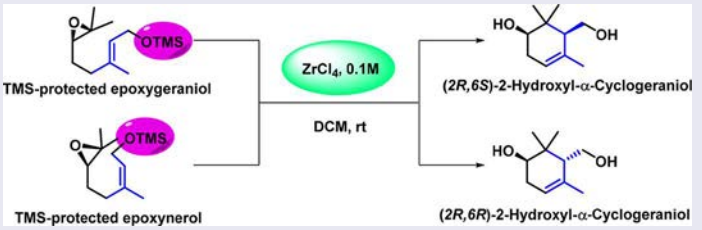
Zi Wang[a], Weiyi Qi[b], Yixuan Yan[c], Youhong Hu[b], and Linhua Song[a]

[a]College of Science, China University of Petroleum (East China), Qingdao, China; [b]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China; [c]School of Pharmacy Lanzhou University, Lanzhou, Gansu, China

ABSTRACT

A cyclization reaction of the hydroxyl-protected geraniol epoxide induced by the different Lewis acids to generate 2-hydroxyl-α-cyclogeraniol has been explored. Compared with the previous methods, this method enhances the production and selectivity of this reaction without the consumption of a large amount of solvent. Also, the coordination of the metal with two oxygen atoms of hydroxyl groups might be crucial for the reaction is first addressed.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 5 July 2016

KEYWORDS
concentration; cyclization; 2-Hydroxyl-α-cyclogeraniol; Lewis acids; protecting groups

Introduction

2-Hydroxyl-α-cyclogeraniol, which derives from inexpensive geranyl acetate, is an important intermediate in the total synthesis of many natural products, e.g., R-damascone,[1] (+)-apotrisporin E,[2] and (–)-karahana ether[3] (Fig. 1). Also, the structure of this unit was found in a large variety of substances, such as taxol,[4] achilleol A,[5] and cordiaquinones C,[6g] which exhibit potent biological activities (Fig. 1).

Although electrophilic cyclization induced by Lewis acid was chosen as an efficient synthetic method to construct terpenoids and other cyclic compounds,[6] few methods devised to synthesize 2-hydroxyl-α-cyclogeraniol involved the cyclization of geraniol epoxide with unsatisfied results (Scheme 1). For example, zirconium tetrachloride mediated the cyclization of geraniol epoxide to produce 2-hydroxyl-α-cyclogeraniol by carrying out at low concentration (approximately ca. 0.007 M of substrate)[7] (Scheme 1, A). It means to scale up the reaction by consuming large amounts of solvent and operate

CONTACT Linhua Song 281170984@qq.com College of Science, China University of Petroleum (East China), Qingdao, 266580, China.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data (full experimental details, ^{1}H and ^{13}CNMR spectra, HRMS, and x-ray crystal data) can be accessed on the publisher's website.

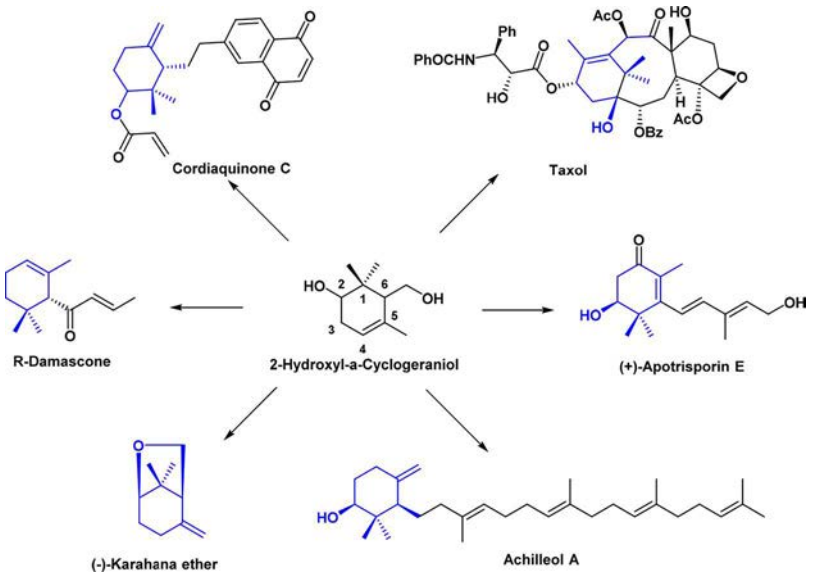
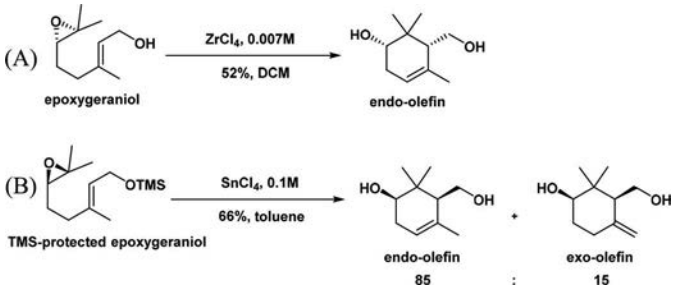


Figure 1. Natural products and bioactive related compounds with the cyclogeraniol core.



Scheme 1. Previous methods to prepare 2-hydroxyl-α-cyclogeraniol.

the synthetic procedure with difficultly. The cyclization of tetramethylsilane (TMS)–protected geraniol epoxide by the treatment of tin tetrachloride affords 2-hydroxyl-α-cyclogeraniol as an endo-olefin with the by-product of exo-olefin, which was hardly separated by chromatography[4] (Scheme 1, B). Moreover, the yields (52–66%) of these reactions still need to be improved. To solve these problems, we herein describe an efficient method to produce 2-hydroxyl-α-cyclogeraniol and its derivatives selectively from hydroxyl-protected geraniol epoxide at high concentration by $ZrCl_4$ or $FeCl_3$. In addition, we disclose the coordination of the metal with two oxygen atoms might be crucial for the selectivity of endo formation, avoiding the ether generation.

Results and discussion

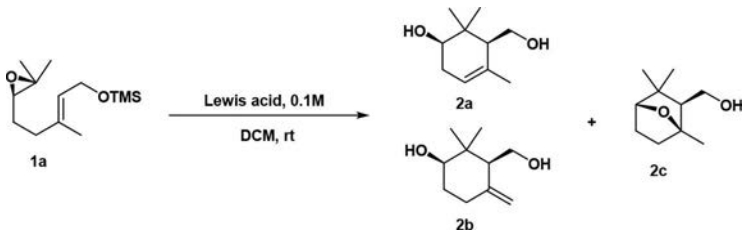
Considering that free hydroxyl group might have an effect on the reaction at high concentration of $ZrCl_4$,[7] we used TMS-protected geraniol epoxide **1a** as the substrate to investigate this reaction. Compound **1a** was synthesized from commercially available

geranyl acetate by Sharpless asymmetric dihydroxylation (85% ee by high-performance liquid chromatography, HPLC), methylsulfonyl chloride–assisted epoxidation and hydroxyl protection with TMS.[4] When treated with 0.5 eq. of $ZrCl_4$ for **1a**, the desired endo-olefin **2a** was obtained in 50% yield with minor cycle inner ether **2c** (Table 1, entry 1).

Encouraged by the result described, we examined the effect of equivalents and classes of Lewis acids. An exploration of different equivalents of $ZrCl_4$ uncovered that the reaction induced by insufficient $ZrCl_4$ could produce minor cycle ether **2c** (Table 1, entries 1 and 2). However, more than 1.0 equiv. of $ZrCl_4$ would decrease the yield of **2a** and cause the reaction complicated (Table 1, entries 4 and 5). One equiv. of $ZrCl_4$ provided the efficient reaction to give endo-olefin **2a** in high yield without **2c** (Table 1, entry 3). Surprisingly, the metallic atom of the Lewis acid containing multiple empty electronic orbitals, such as $ZrCl_4$, $FeCl_3$, $TiCl_4$ (Table 1, entries 3, 6, and 7), generates endo-olefin **2a** as the sole product. In contrast, the other Lewis acid (Table 1, entries 9–12) possessing fewer empty orbitals could produce a certain amount of cycle ether **2c**. Moreover, the reaction induced by $ZrCl_4$ or $FeCl_3$ did not form exo-olefin comparing with $SnCl_4$. Noteworthy, $FeCl_3$ as the cheap and environmentally friendly Lewis acid can also promote cyclization of epoxide to endo-olefin efficiently. When 2 mol% of TfOH was tested in the cyclization, only the deprotection of substrate occurred (Table 1, entry 13).

Subsequent studies for among different concentrations of substrate **1a** showed that the yield of the reaction would be decreased by the increasing the concentration of the substrate using $ZrCl_4$ or $FeCl_3$ as Lewis acid (Table 2, entries 1–3). Also, reducing reaction temperature (Table 2, entries 4 and 5) or using some other solvent, such as hexane, toluene,

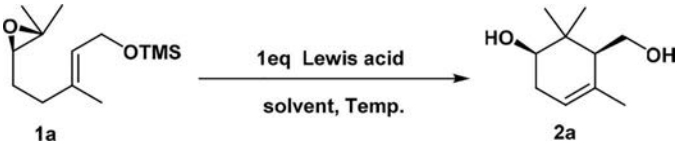
Table 1. Optimization of acid for the cyclization of **1a**.[a]



Entry	Acid	Eq.	2a and 2b Yield[b] (%)	2a and 2b Ratio[c]	Yield of 2c[b] (%)
1	$ZrCl_4$	0.5	50	100:0	19
2	$ZrCl_4$	0.75	68	100:0	7
3	$ZrCl_4$	1	80	100:0	—
4	$ZrCl_4$	1.5	66	100:0	—
5	$ZrCl_4$	2	Complicated	—	—
6	$FeCl_3$	1	76	100:0	—
7	$TiCl_4$	1	38	100:0	—
8	$SnCl_4$	1	62	81:19	—
9	$InBr_3$	1	24	100:0	19
10	$AlCl_3$	1	32	78:22	35
11	BF_3•Et_2O	1	31	77:23	28
12	$ZnCl_2$	1	33	66:33	16
13	TfOH	0.02	Deprotection		—

[a]Unless otherwise noted, reactions were carried out under the standard conditions.
[b]Yield of isolated product based on **1a** of 0.5-mmol scale.
[c]Determined by ^{1}H NMR.

Table 2. Optimizing for the concentration of epoxide **1a**, reaction temperature, and solvent.[a]



Entry	Lewis acid	Temp.	Solvent	Concentration of **1a** (M)	Yield[b] (%)
1	$ZrCl_4$	rt	DCM	0.2	69
2	$ZrCl_4$	rt	DCM	0.5	44
3	$FeCl_3$	rt	DCM	0.2	66
4	$ZrCl_4$	0 °C	DCM	0.1	63
5	$ZrCl_4$	−20 °C	DCM	0.1	41
6	$ZrCl_4$	rt	Hexane	0.1	39
7	$ZrCl_4$	rt	Toluene	0.1	75
8	$ZrCl_4$	rt	CH_3CN	0.1	38
9	$ZrCl_4$	rt	THF	0.1	Deprotection
10	$ZrCl_4$	rt	DMF	0.1	Complicated
11	$ZrCl_4$	rt	DMSO	0.1	Complicated

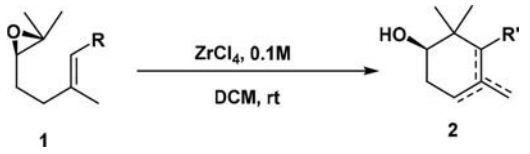
[a]Unless otherwise noted, reactions were carried out under the standard conditions.
[b]Yield of isolated product based on **1a** of 0.5-mmol scale.

and acetonitrile (Table 2, entries 6–8) would decrease the yield. Probably owing to the effect of oxygen in tetrahydrofuran (THF) on Lewis acid, when using THF as solvent, only the deprotection of **1a** occured (Table 2, entries 9). In addition, solvent DMF or DMSO, which contain acyl or sulfinyl, would totally complicate the cyclization (Table 2, entries 10 and 11).

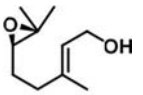
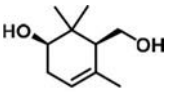
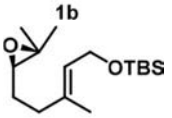
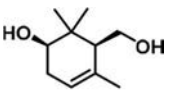
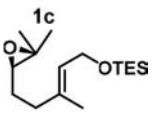
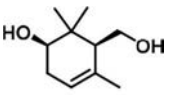
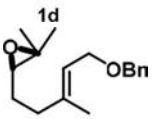
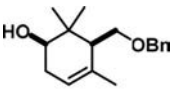
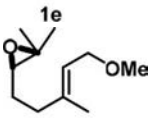
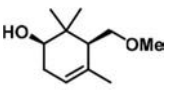
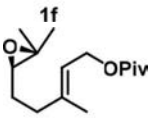
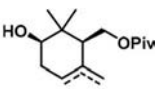
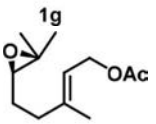
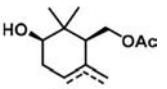
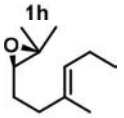
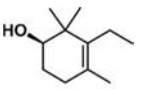
Next, we applied the optimized condition to various hydroxyl protected epoxides **1** to find the correlation of the reaction with another oxygen. As expected, **1b** without a protecting group gives **2a** in low yield, accompanied by complicated products as reported before.[7] The different silyl protecting group for hydroxyl could afford **2a** in the moderate yields (Table 3, entries 2 and 3). Obviously, the steric hindering effect impacts the reaction dramatically. With the alkoxy group, the substrate **1e** or **1f** could also be transformed to the corresponding product in good yield efficiently and selectively (Table 3, entries 4 and 5). However, the reaction that acyl group was selected as a protecting group (Table 3, entries 6 and 7) generated the endo-olefin along with exo-olefin in low yield. In addition, when replacing hydroxy of substrate with methyl, only minor tetra-substituted olefin **2i** was generated (Table 3, entry 8). From these results, the factors of Lewis acid possessing multiple empty orbitals together with the protected hydroxy play important roles in the cyclization to produce the desired endo-olefin **2**.

To explain this results and the configuration of the product, we proposed the mechanism shown in Scheme 2. At first, epoxide **1a** is cleaved under the inducement of zirconium tetrachloride to produce cationic species **M1**, which undergoes π-electron pair transfer to cyclic intermediate **M2**. Because of the multiple empty orbitals of zirconium, the metal could strongly coordinate with two oxygen atoms to constitute part of the potential favorable six-membered ring, which can stabilize carbocation **M2** and prevent the formation of cyclic ether. It may be the reason that employing the Lewis acid insufficiently (Table 1, entries 1 and 2) or the other Lewis acid without enough empty orbitals (Table 1, entries 9–12) formed the internal ether. Moreover, the electron-withdrawing and steric hindering group would decrease the effect of coordination between zirconium and oxygen atoms of hydroxyl groups, and then restrained the formation of six-membered ring to afford the endo-olefin **2** in lower yield (Table 3, entries 6 and 7). Analogously, the yield of reaction that involved

Table 3. Effect on the different R groups for the cyclization.[a]



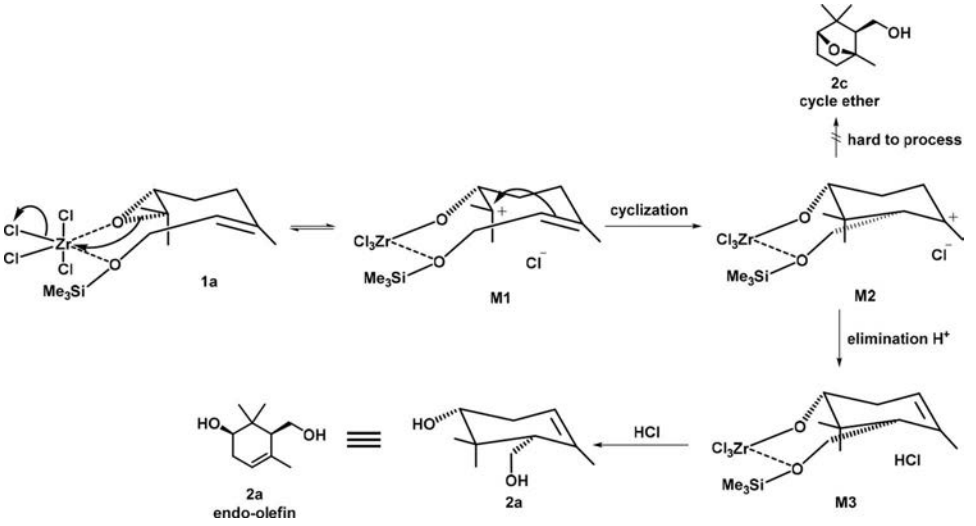
1 2

Entry	1	Yield of 2[b] (%)	2
1		25	
	1b		2a
2		59	
	1c		2a
3		63	
	1d		2a
4		67	
	1e		2e
5		66	
	1f		2f
6		13	
	1g		2g endo/exo=100:11[c]
7		17	
	1h		2h endo/exo=100:7[c]
8		15	
	1i		2i

[a]Unless otherwise noted, reactions were carried out under the standard conditions.
[b]Yield of isolated product based on 1 of 0.5-mmol scale.
[c]Determined by ^{1}H NMR.

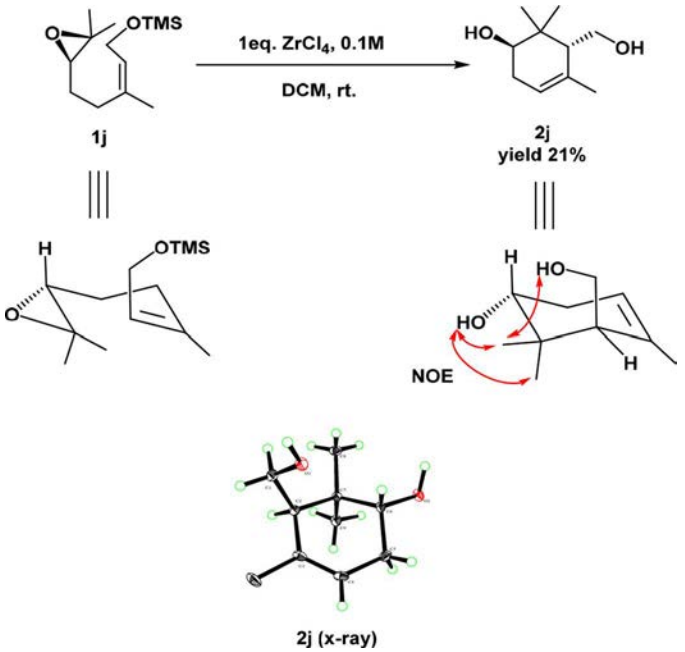
1i without hydroxyl oxygen selected as substrate was lower (Table 3, entry 8), probably because the formation of six-membered ring could be totally prevented. After favorable β-elimination of proton of **M2**, corresponding olefin **2a** can be generated.

Under the optimized reaction conditions, we also investigated the ability of $ZrCl_4$ to promote the cyclization reaction of chiral epoxyneryl ether **1j**, which was synthesized from



Scheme 2. Proposed mechanism.

neryl acetate by the similar procedure. The compound **2j** is the transformation by the analysis of nuclear Overhauser effect (NOE) spectra and further confirmed by x-ray crystallographic analysis[8] (Scheme 3). According to the proposed mechanism, the desired product **2j** was obtained in a reasonable, low yield due to axial TMS-carbinol group of **1j**, which prevented the formation of Zr-O six-membered ring.



Scheme 3. Cyclization of epoxyneryl ether **1j** to trans-diol **2j**.

Conclusion

In conclusion, we have developed an efficient and solvent-saving electrophilic cyclization of the hydroxyl-protected geraniol epoxide, which promoted by zirconium tetrachloride or ferric trichloride. Notably, the factors of Lewis acid possessing multiple empty orbitals together with the protecting group for hydroxyl play important roles in the cyclization to produce the desired endo-olefin **2**. We first proposed that the coordination of the metal with two oxygen atoms of hydroxyl groups might be crucial for the reaction. Under the optimized reaction condition, (*2R,6R*)-2-hydroxyl-α-cyclogeraniol **2j** was synthesized and confirmed by x-ray crystallographic analysis. This efficient and easily operational method could be applicable to the preparation of intermediate of numerous natural products and bioactive molecule.

Experimental

All reactions were performed in oven-dried flask containing a septum and Teflon-coated stirrer bar under a nitrogen atmosphere. All ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or d-DMSO with TMS as the internal standard. Chemical shifts are expressed in parts per million (ppm) and J values are given in hertz (Hz). Infrared (IR) spectra were obtained on a Lumex Infralum FT-02 spectrometer with absorption in cm^{-1}. Column chromatography was performed with 200- to 300-mesh silica gel.

Standard condition for preparing 2a

$ZrCl_4$ (117 mg, 0.5 mmol) was added to a solution of **1a** (121 mg, 0.5 mmol) in dry DCM (5 mL) at room temperature under nitrogen atmosphere. After stirring for 1 h, 1.0 M HCl (5 mL) was added and the two layers were separated. The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (PE/EA = 3) to afford **2a** (68 mg, 80%).

(2R,6S)-2-Hydroxyl-α-cyclogeraniol (2a)

R*f* = 0.42 (stained by PMA, PE/EA = 2:1). IR (KBr, cm^{-1}): 3226, 2975, 2919, 2884, 1713, 1674, 1472, 1036, 906. ^{1}H NMR (500 MHz, chloroform-*d*) δ 5.49 (ddq, *J* = 5.3, 2.7, 1.4 Hz, 1H), 3.81 (d, *J* = 2.5 Hz, 2H), 3.66 (d, *J* = 43.4 Hz, 2H), 3.44 (d, *J* = 4.8 Hz, 1H), 2.42 (ddq, *J* = 18.7, 5.0, 2.5 Hz, 1H), 2.15 (dddd, *J* = 18.6, 4.3, 2.6, 1.3 Hz, 1H), 1.79 (h, *J* = 1.2 Hz, 3H), 1.77 (s, 1H), 1.14 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 131.62, 120.42, 71.41, 58.81, 51.10, 37.16, 32.28, 28.62, 24.36, 22.61. HRMS (EI) calcd. for $[M]^+$: 170.1307; found: 170.1306.

Funding

The authors thank the National Natural Science Foundation of China (81225022) for financial support.

References

[1] Bovolenta, M.; Castronovo, F.; Vadala, A.; Zanoni, G.; Vidari, G. *J. Org. Chem*. **2004**, *69*, 8959.
[2] Gonzalez-Delgado, J. A.; Arteaga, J. F.; Herrador, M. M.; Barrero, A. F. *Org. Biomol. Chem*. **2013**, *11*, 5404.
[3] Serra, S.; Gatti, F. G.; Fuganti, C. *Tetrahedron: Asymmetry* **2009**, *20*, 1319.
[4] Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *J. Org. Chem*. **1995**, *60*, 7209.
[5] Barrero, A. F.; Alvarez-Manzaneda, E. J. R.; Alvarez-Manzaneda R, R. *Tetrahedron Lett*. **1989**, *30*, 3351.
[6] (a) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc*. **2009**, *131*, 13928–13929; (b) Garcia Santos, W. H.; Puerto Galvis, C. E.; Kouznetsov, V. V. *Org. Biomol. Chem*. **2015**, *13*, 1358; (c) Smith, B. M.; Skellam, E. J.; Oxley, S. J.; Graham, A. E. *Org. Biomol. Chem*. **2007**, *5*, 1979; (d) Li, H.; Sun, Y.; Zhang, Q.; Zhu, Y.; Li, S. M.; Li, A.; Zhang, C. *Org. Lett*. **2015**, *17*, 306; (e) Shenvi, R. A.; Corey, E. J. *Org. Lett*. **2010**, *12*, 3548; (f) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett*. **1991**, *32*, 7005; (g) Arkoudis, E.; Stratakis, M. *J. Org. Chem*. **2008**, *73*, 4484.
[7] Vidari, G.; Beszant, S.; El Merabet, J.; Bovolenta, M.; Zanoni, G. *Tetrahedron Lett*. **2002**, *43*, 2687.
[8] CCDC 1431014; see the supplementary data to find x-ray crystal data.