A stereoselective approach for the total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide

Gembali Manikanta, Palakodety Radha Krishna

PII: S0040-4039(18)30739-1
DOI: https://doi.org/10.1016/j.tetlet.2018.06.010
Reference: TETL 50048

To appear in: *Tetrahedron Letters*

Received Date: 7 May 2018
Revised Date: 31 May 2018
Accepted Date: 3 June 2018

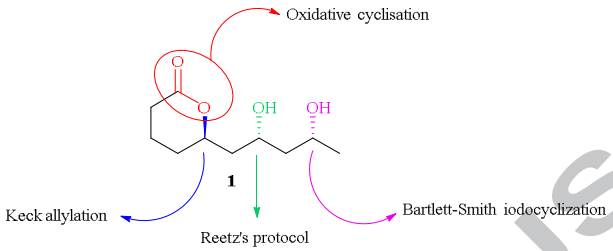
Please cite this article as: Manikanta, G., Radha Krishna, P., A stereoselective approach for the total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.010

Graphical Abstract

A stereoselective approach for the total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide

Gembali Manikanta and Palakodety Radha Krishna*

Leave this area blank for abstract info.



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A stereoselective approach for the total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide

Gembali Manikanta and Palakodety Radha Krishna*

D-211, Discovery Laboratory, Organic & Biomolecular Chemistry Division

CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

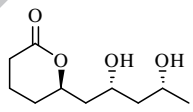
Keywords:
Total synthesis,
Lactones,
Bartlett–Smith halocyclization,
Oxidative lactonization.

ABSTRACT

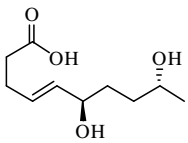
A stereoselective approach for the total synthesis of lactone (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide is described. The sequence of synthetic reactions involves a Keck asymmetric allylation, diastereoselective iodo-carbonate cyclization, regioselective ring-opening reaction, oxidative lactonization.

Introduction

δ-Lactone is a common structural motif among many classes of natural products, some of which exhibit striking biological properties.[1] Recently Yoshihito Shiono and co-workers isolated δ-lactone containing polyketide natural product (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide **1** from rice cultures of *Cylindrocarpon* sp. SY-39 along with another compound (4*E*,6*R*,9*R*)-6,9-dihydroxydec-4-enoic acid (**2**).[2] The biological activity of compound **1** has not been fully evaluated, compound **2** exhibited moderate antimicrobial activity against *Staphylococcus aureus* NBRC 13276 and *Aspergillus clavatus* F 318a at a concentration of 50 μg per disk.[2] As part of our research program targeting on the synthesis of lactone containing natural products, earlier we reported total synthesis of some lactone containing molecules.[3] In continuation, herein we describe the stereoselective approach to the total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide.[2]

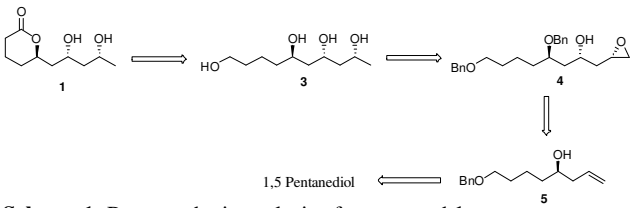


1



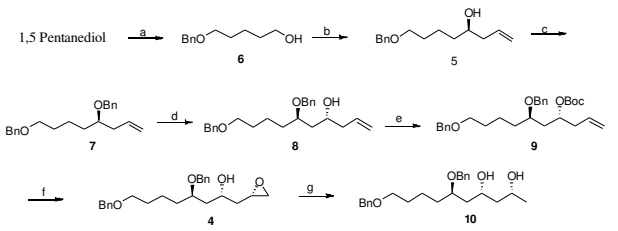
2

The envisaged retrosynthetic strategy for compound **1** is delineated in Scheme **1**. A linear synthetic strategy was invoked wherein compound **1** was accessed from oxidative lactonization of corresponding acid obtained from **3**, that might be prepared by regioselective ring-opening of epoxide **4** followed by dibenzyl deprotection. The epoxy alcohol **4** might in turn be obtained from chiral homo allylic alcohol **5**, that could be prepared from commercially available 1, 5 Pentanediol by a sequential traditional steps.



Scheme 1: Retrosynthetic analysis of compound **1**

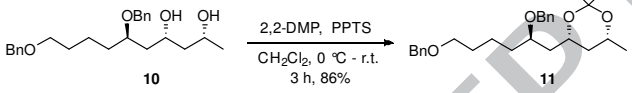
Accordingly, the synthesis of **1** commencing from the monoprotected 1,5-pentanediol **6**[4] is shown in Scheme 2. The primary alcohol function in **6** oxidized under Swern conditions to give the aldehyde, which was immediately subjected to the Keck asymmetric allylation with (*S*)-BINOL, 4 Å MS, $Ti(O^iPr)_4$, allyltributylstannane, CH_2Cl_2, -78 °C to -20 °C, to afford homo allylic alcohol **5** in 80% yield (two steps) and 96% ee. All the spectral data of alcohol **5** matched with the reported values of an enantiomer but the optical rotation had the opposite sign.[5] The newly formed hydroxy group in **5** was protected with benzyl bromide in the presence of sodium hydride in THF to afford the dibenzyl compound **7** in 87% yield. The one-pot oxidative cleavage of the terminal double bond in **7** with OsO_4-$NaIO_4$ and 2,6-lutidine in dioxane-water (3:1)[6] afforded the desired aldehyde, which was immediately treated with allyltrimethylsilane in the presence of titanium tetrachloride in CH_2Cl_2 at –78 °C according to Reetz's protocol[7] to give the *anti* 1,3-homoallylic alcohol **8** stereoselectively in 73% yield (two steps). All the spectral data of this compound matched with our earlier data.[4]



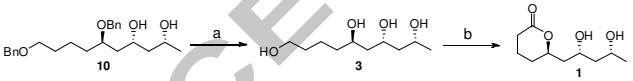
Scheme 2. *Reagents and conditions:* (a) Ref. 4; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h (ii) *S*-BINOL, $Ti(O^iPr_4)$, allyltributyltin, CH_2Cl_2, -78 °C, 80% (over two steps); (c) BnBr, NaH, THF, 0° C to r.t., 87%; (d) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1, 4-dioxane:water (3:1), r.t.; (ii) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, –78 °C, 1 h, 73% (over two steps); e) $(Boc)_2O$, DMAP, CH_2Cl_2, r.t., 5 h, 88%; (f) NIS, CH_3CN, -40 to 0 °C, 10 h; (ii) K_2CO_3, CH_3OH, 0 °C to r.t., 2 h, 73 %, (over two steps); (g) $LiAlH_4$, THF, r.t., 2h, 88%.

Next, Boc protection of allylic alcohol **8** with di-*tert*-butyl dicarbonate in the presence of DMAP gave the homoallylic *tert*-butyl carbonate **9** in 88% yield. Compound **9** was subjected to the Bartlett-Smith iodo-carbonate cyclization[8] with NIS in CH_3CN to furnish the cyclic carbonate derivative, which on treatment with K_2CO_3 in CH_3OH delivered the desired *syn*-epoxy alcohol **4** in 73% yield (two steps). Regioselective reductive opening of epoxide **4** using $LiAlH_4$ in THF furnished *syn*-1,3-diol **10** in 88% yield.

The relative stereochemistry of the 1,3-diol system in **10** was determined by Rychnovsky's analogy.[9] Thus, treatment of diol **10** with 2,2-DMP in the presence of PPTS in CH_2Cl_2 at room temperature gave the *syn*-acetonide **11** (86% yield). The ^{13}C NMR of **11** showed signals assigned to the acetonide methyl group at δ = 19.9 and 30.3 ppm and quaternary carbon resonated at 98.3 ppm in accordance with Rychnovsky's[9] model for a 1,3-*syn* relationship between the acetonide-attached carbons. Thus the relative stereochemistry of the newly created stereogenic center was unequivocally assigned as *syn* to the existing one and the absolute stereochemistry of the newly created stereogenic carbon could be assigned as '*R*'.



In the next stage debenzylation of compound **10** under H_2 and 10% Pd-C in CH_3OH for 3 h at room temperature gave the tetrol **3** (86% yield) which was lactonized in a single step by selective oxidation of the primary alcohol to its corresponding acid with TEMPO and [bis(acetoxy)iodo]benzene in CH_2Cl_2, H_2O (3:1) followed by cyclization to afford the target molecule **1** in 75% yield.



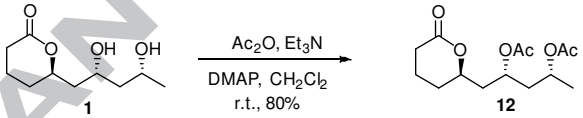
Scheme 3: *Reagents and conditions*: (a) H_2, 10% Pd-C, CH_3OH, r.t., 3h, 86%; (b)TEMPO, BIAB, CH_2Cl_2:H_2O (3:1), r.t., 1 h, 75%.

Table 1. ^1H and ^{13}C data of natural product and synthetic compound.

Position	Natural product		Synthetic product (**1**)	
	δ ^{13}C NMR	^1H NMR	δ ^{13}C NMR	^1H NMR
1	177.2		172.3	
2,4,6,8	28.1, 34.7	1.79-1.82 m	25.0, 30.2	1.60-1.82 m
	43.3, 36.5	1.86-1.93 m	47.7, 45.4	1.86, 1.97 m
		2.12-2.20 m		
3	28.8	2.40-2.45 m	29.2	2.44, 2.54m
7	67.7	3.99 m	67.5	4.33 m
9	67.1	4.04 m	67.2	4.49 m
5	78.9	4.90 quin	77.6	4.87 m
10	24.1	1.32 d	19.2	1.37 d

Surprisingly, the ^1H and ^{13}C NMR spectroscopic data of synthetic compound **1** are not in consistent with the reported data of natural product.[2] Thorough examination of the ^1H NMR data of the synthetic compound **1** revealed contrasting chemical shift differences of key hydrogens when compared to the natural product. Remarkably the hydrogens attached to the stereogenic centres H9 and H7 appeared upfield in the synthetic product (Table 1). Moreover, some minor differences between other hydrogens and several carbon chemical shifts were also found (Table 1).

To corroborate the structure assigned of the synthetic product further, we resorted to chemical correlation method. The diacetate of compound is already known in the literature.[10] Hence, compound **1** was converted into its diacetate under standard conditions to obtain **12** (80%). The ^1H and ^{13}C NMR spectra and other physical data of our synthetic compound **12** was in complete agreement with literature data.[10] The comparative chemical analysis of compound **12** with literature data confirmed the absolute stereochemistry of synthetic **12** as (5*R*,7*R*,9*R*) and since **12** was obtained from **1**, extending the argument we thus established the structure of synthetic compound **1** as (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide and is constitutionally correct. It is therefore likely that the spectral discrepancies are due to stereochemical misassignments of the natural product.



In summary, we accomplished the linear, stereocontrolled total synthesis of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide.[1] The key features of the synthesis include asymmetric Keck allylation, Bartlett-Smith iodocyclization, regioselective ring opening of epoxide and oxidative lactonization. The differences in the spectral data between synthetic **1** and natural product strongly suggested a structural misassignment during the isolation of (5*R*,7*R*,9*R*)-7,9-dihydroxy-5-decanolide and a structural revision is thus warranted.

Acknowledgements

One of the authors (G. M) is thankful to the UGC, New Delhi for financial support in the form of fellowship. IICT/Pubs/2018/158.

References

1. (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912-4915. b) Drewes, S. E.; Sehlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry.* **1995**, *38*, 1427-1430.

2. Yoshidaa, S.; Suzukia, T.; Furunob, H.; Aboshia, T.; Murayamaa, T.; Kosekia, T.; Shiono, Y. *Nat. Prod. Research.* **2018**, *32*, 60–64.

3. (a) Radha Krishna, P.; Ramana Reddy, V. V. *Tetrahedron Lett.* **2005**, *46*, 3905-3907. (b) Radha Krishna, P.; Srinivas Reddy, P. *Tetrahedron.* **2007**, *63*, 3995-3999. (c) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett*. **2007**, *48*, 2013-2015. (d) Radha Krishna, P.; Srinivas, R. *Tetrahedron: Asymm.* **2007**, *18*, 2197-2200. (e) Radha Krishna, P.; Srinivas, P. *Tetrahedron Lett.* **2010**, *51*, 2295-2296. (d) Radha Krishna, P.; Rajesh, N.; Ramesh, k. *Synthesis.* **2014**, *46*, 307-312. (e) Dayaker, G.; Radha Krishna, P. *Helv. Chem. Acta*. **2014**, *97*, 868-880. (f) Manikanta, G.; Raju, G.; Radha Krishna, P. *RSC Adv*. **2015**, *5*, 7964-7969. (g) Manikanta,

G.; Nagaraju, T.; Radha Krishna, P. *Synthesis* **2016**, *48*, 4213-4220.

4. Raju, G.; Anitha, K.; Radha Krishna, P. *Synlett* **2015**, *26*, 937-941.

5. (a) Tony, K. A.; Dabideen, D.; Li. J.; Díaz-Hernández, M. D.; Jiménez-Barbero, J.; Mootoo, D. R. *J. Org. Chem.* **2009**, *74*, 7774-7780. (b) Yadav, J.S.; Swapnil, N.; Venkatesh, M.; Prasad, A.R. *Tetrahedron Lett.* **2014**, *55*, 1164-1167.

6. Yu,W.; Mei,Y.; Kang, Y.; Hua, Z.; Jin, Z.; *Org. Lett.* **2004**, *6*, 3217-3219.

7. (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833-4835. (b) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729-732. (c) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606-6611.

8. Barrlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013-4018.

9. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7103; (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.

10. Yamauchi, S.; Nishimura, H.; Nishiwaki, H. *Biosci. Biotechnol. Biochem.* **2015**, *79*, 16-24.

11. For spectral data and experimental procedures, please see *Supporting Information.*

HIGHLIGHTS

- δ-Lactone natural product
- Keck asymmetric allylation
- Iodo-carbonate cyclization