Studies towards the total synthesis of (+)-13-deoxytedanolide: stereoselective synthesis of C1-C9 and C9-C17 fragments

Jhillu Singh Yadav, Vijaya Vardhan Chinnam, Saibal Das

PII: S0040-4039(15)30516-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.12.101
Reference: TETL 47148

To appear in: *Tetrahedron Letters*

Received Date: 10 November 2015
Revised Date: 7 December 2015
Accepted Date: 26 December 2015

Please cite this article as: Yadav, J.S., Chinnam, V.V., Das, S., Studies towards the total synthesis of (+)-13-deoxytedanolide: stereoselective synthesis of C1-C9 and C9-C17 fragments, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.101

Tetrahedron Letters
journal homepage: www.elsevier.com

Studies towards the total synthesis of (+)-13-deoxytedanolide: stereoselective synthesis of C1-C9 and C9-C17 fragments

Jhillu Singh Yadav*[a] Vijaya Vardhan Chinnam,[a] and Saibal Das[a]

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

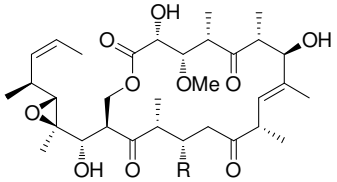
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
(+)13–Deoxytedanolide
cytotoxic metabolite
Sharpless Asymmetric Dihydroxilation
Sharpless epoxidation
Crimmin's syn aldol

ABSTRACT

A facile and stereoselective synthesis of C1–C9 and C9–C17 fragments of (+)-13-deoxytedanolide and studies towards the synthesis of (+)-13-deoxytedanolide was accomplished in 20 linear steps. The key transformations of fragment **6** are Sharpless asymmetric dihydroxylation and preperation of terminal olefin from primary alcohol utilising organo selenium reaction. The key transformations of fragment **7** are from Sharpless epoxidation and Crimmin's syn aldol chemistry.

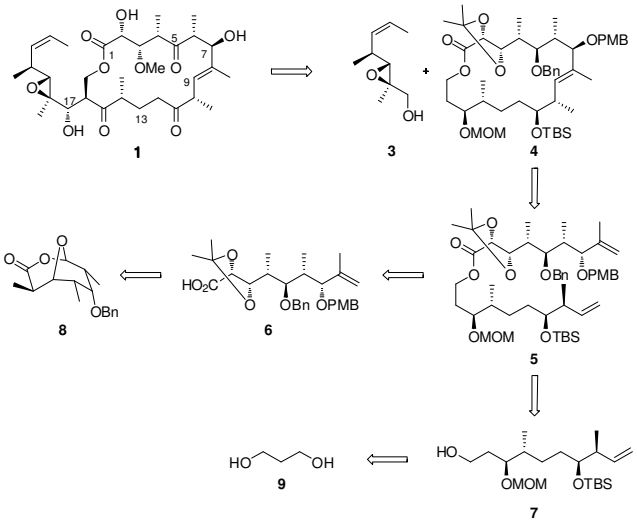
13–Deoxytedanolide **(1)**, a known cytotoxic metabolite isolated from the Japanese marine sponge *Mycale adharens* by Fusetani et al.[1] in 1991. Tedanolide **(2)**, parent molecule of (+)-13-deoxytedanolide **(1)**, was isolated from the Caribbean sponge *Tedania ignis* in 1984 by Schmitz et al.[2] Both show a remarkable cytotoxicity against P388 murine leukaemia cells at pico to nano molar ranges. Moreover, (+)-13-deoxytedanolide **(1)** has been shown to have promising in vivo antitumor activity. Fusetani et al. identified 13-deoxytedanolide **(1)** bound to the 60S large ribosomal subunit of the budding yeast *Saccharomyces cerevisiae*, thus inhibiting polypeptide elongation and is the first macrolide inhibitor for the eukaryotic ribosome.[3] Owing to the combination of architectural complexity and bioactivity various research groups have shown wide interest for the syntheses of Tedanolides.[4] Smith and Roush independently reported the two total syntheses of (+)-13-deoxytedanolide (**1**) in 2003 and 2005 respectively.[5]



(+)-13-deoxytedanolide (**1**) R=H

(+)-tedanolide (**2**) R=OH

Figure 1. Structure of 13–deoxytedanolide (**1**)

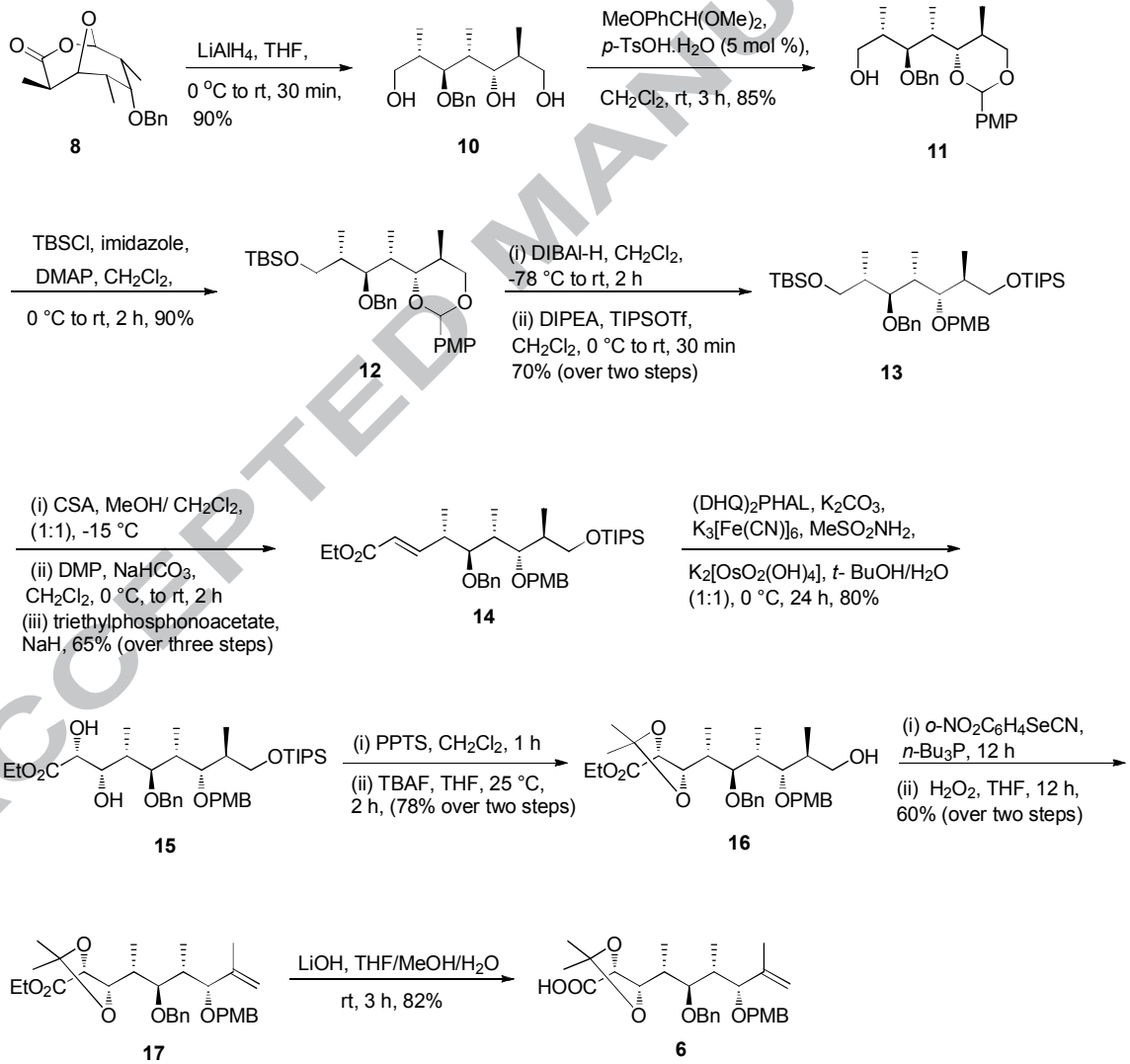


Scheme 1. Retrosynthetic steps for vittarilide-A **(1)**

In 2011, our group reported the syntheses of two fragments of C_1–C_9 and C_9–C_{17}, based on the application of Sharpless asymmetric dihydroxylation and Crimmins' *syn* aldol reaction respectively.[6] Futher to our refine our previous work in decreasing number of steps we derived new strategy for the synthesis of **6** and **7** fragments. In order to achieve the fragment **6** we employed Sharpless asymmetric dihydroxylation and

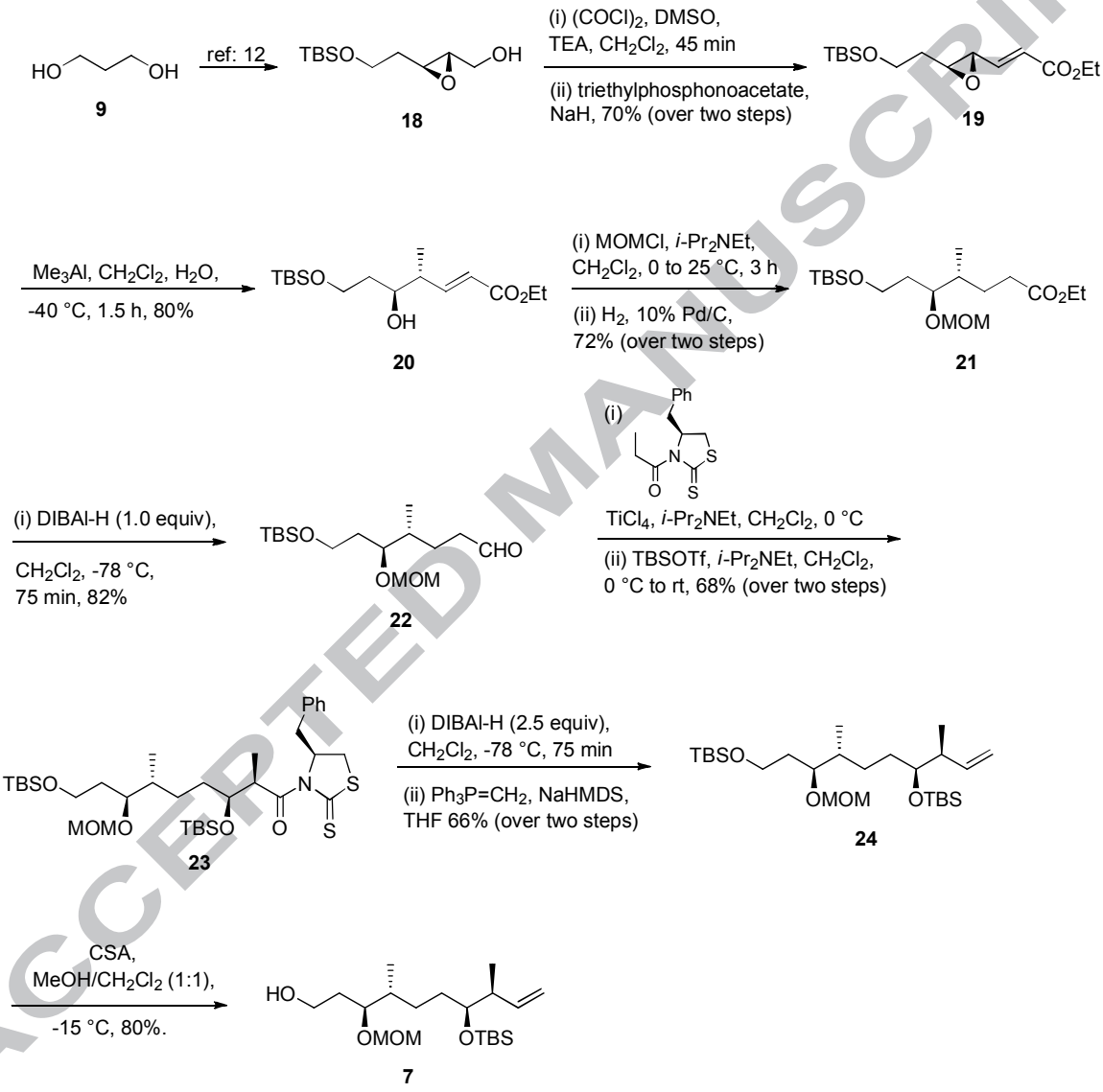
fragment **7** the Sharpless epoxidation and Crimmins' *syn* aldol reactions were adopted. We further made trials to make 18 membered macrolactone core **4** from fragments **6** and **7** as a part of the total synthesis of (+)-13-deoxytedanolide. The retrosynthetic strategy was the fragment **6** was obtained from lactone **8** and alcohol **7** could be derived from propanediol **9** via Sharpless epoxidation and non–Evans' aldol reactions.

We initiated the our work by the synthesis of fragment **6** which was initiated with reductive opening of the lactone **8**[6] using $LiAlH_4$ in dry THF to afford the triol **10** in which 1, 3-diol was protected as PMB acetal with p–methoxybenzyl dimethyl acetal and catalytic amount of CSA in CH_2Cl_2 gave the compound **11** in 85% yield.[7] The primary hydroxyl group of **11** was protected as TBS ether to furnish the compound **12** in 90% yield. The regioselective reduction of PMB acetal to PMB ether using DIBAL-H[8] followed by silylation of primary alcohol using TIPSOTf and DIPEA in CH_2Cl_2 yielded the compound **13** in 70% yield (over two steps). Selective deprotection of TBS group in compound **13** using catalytic amount of CSA in $MeOH/CH_2Cl_2$ in 1:1 ratio[9] followed by sequential steps involving Swern oxidation followed by Witting olefination furnished the corresponding α,β- unsaturated ester **14** in 65% yield (over three steps). The olefin was subjected to Sharpless asymmetric dihydroxylation (SAD)[10] conditions employing potassium osmate (5 mol%) and potassium ferricyanide as a co-oxidant in the presence of a $(DHQ)_2PHAL$ ligand (10 mol%) to furnish the corresponding 1, 2-diol **15** in 80% yield and 92% de. The 1,2-diol compound **15** was protected as its acetonide followed by desilylation of silyl group of TIPS using TBAF provided the primary alcohol **16** in 78% yield (over two steps). Now, the conversion of alcohol to di-substituted olefin is crucial. In previous synthesis our group only demonstrated this conversion using NaI and DBU, but this reaction was not always fruitful for poly hydroxy protected fragments, hence we used the Grieco protocol conditions[11] that, the alcohol was protected as selenyl ether using 2-Nitro selenocyanate and tri *n*-butyl phosphine to furnished the selenium product which was further converted to terminal disubstituted olefin **17** with H_2O_2 in 60% yield for two steps. Finally, the desired acid **6** was afforded by base hydrolysis of ester using $LiOH.H_2O$ in $THF/MeOH/H_2O$ in 4:1:1 ratio in 82% yield.



Scheme 2. Synthesis of acid fragment **(6)**

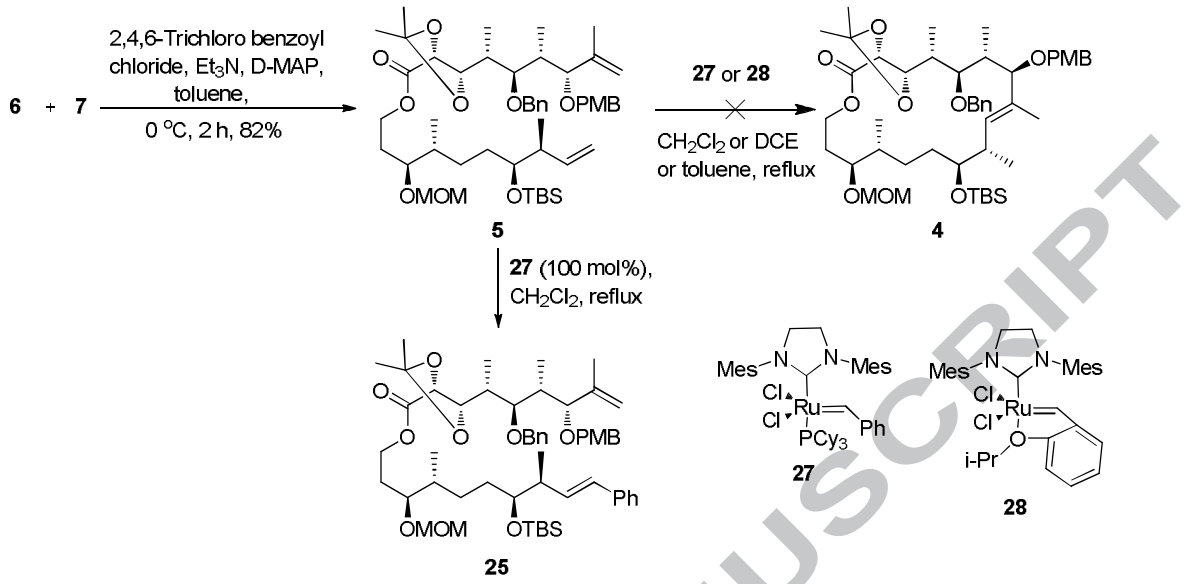
The synthesis of fragment **7** was initiated with commercially available propane diol **9** which was subjected to sequential reactions to give **18** (see ref:12) in 80% yield in five steps. The oxidation of alcohol **18** using Swern oxidation condition yielded the required aldehyde followed by Horner Wittig condition with NaH and triethyl phosphano acetate afforded the epoxy ester **19** in 70% yield (over two steps).[13] The regioselective opening of epoxide by treating with TMA (Tri Methyl Aluminium) afforded corresponding alcohol **20**[14] in 80% yield which in turn was protected as MOM ether. It was followed by reduction of double bond using Pd/C to furnish the corresponding ester **21** in 72% yield (over two steps).[15] Subsequently, the ester **21** was partially reduced to aldehyde **22** by DIBAl-H which was further subjected to the non-Evans' *syn* aldol[16] using 1 equiv of auxillary *N*-propanoyl thiazolidinone, 1 equiv of $TiCl_4$, 1 equiv of DIPEA and obtained the desired *syn* aldol product as the major isolable diastereomer (de ~95%). The resulting secondary alcohol was protected as TBS ether **23** in 68% yield (over two steps). Silyl compound **23** was achieved by using reduction of the chiral thiazolidinone. With DIBAl-H **23** afforded the required aldehyde[17] which in turn was subjected to Wittig olefination with Ph_3PCH_3I and yielded the terminal olefin **24** in 66% (over two steps). Eventually, selective deprotection of primary TBS using CSA in MeOH/CH_2Cl_2 (1:1) to furnish required fragment **7** in 80% yield.



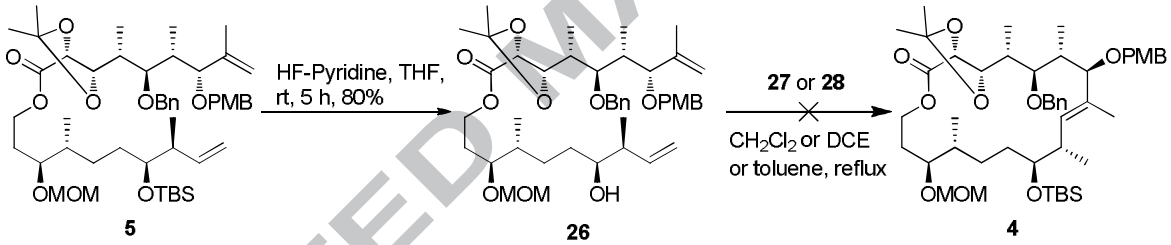
Scheme 3. Synthesis of alcohol fragment **(7)**

Now two fragments in hand, our strategy was to couple the two fragments **6** and **7** to make the lactone **4**. In the process of making of lactone, esterification of fragments **6** and **7** using Yamaguchi condition[18] yielded the corresponding ester **5** in 82% yield. The crucial reaction of coupling of two terminal olefins in which one was the branched olefin posed a challange. In fact, only few reports were seen for such that too coupling was achieved when the branched olefin does not contain substitution at α position. In 2007 Wei-Min Dai *et al.* reported that achievement of RCM between tri-substituted and di-substituted double[19] bonds by addition of Grubbs' second generation catalyst **27** in portion wise (total amount equal to 100 mol%) in CH_2Cl_2 under refiux condition. They obtained the required product and by-product in 1:1 ratio. We applied

the similar reaction conditions but we observed the formation of by-product **25** only, which might be due to the hindrance of stereomers and protection groups adjacent to tri-substituted double bond.



Scheme 4. Synthesis of ester intermediate **(5)**



Scheme 4. Synthesis of ester intermediate **(26)**

Therefore, it was felt worthwhile to deprotect the silyl groups by desilylation of **5** and attempt the RCM reaction with the resulting allylic alcohol **26**. However, the RCM of **26** with 10 mol% of Grubbs' second generation catalyst **27** in CH_2Cl_2 in refluxing conditions yilded no reaction and compound **26** as such with out a trace of desired compound **4**.Then we made several trails with Hoyeda-Grubbs' second generation catalyst **28** in different solvent conditions like dichloro ethane and toluene under reflux condition, however we did not observe any progress and only starting material was recovered.

In conclusion, we have accomplished the highly stereoselective synthesis of **6** and **7** fragments of (+)-13-deoxytedanolide **(1)** in a concise manner using Sharpless asymmetric dihydroxylation, Sharpless epoxidation and Crimmins' *syn* aldol and esterification under Yamaguchi conditions as key steps with an overall yield 4.2%.

Acknowledgements

C. V. V thanks CSIR, New Delhi, India for fellowship. The authors thank CSIR, New Delhi for financial support through Project ORIGIN under 12th Five Year Plan and J. S. Y. thanks CSIR and Department of Science and Technology (DST), New Delhi for the award of Bhatnagar and J. C. Bose Fellowships**.**

Supplementary data

Experimental procedures, Spectral data and Copies of ^{1}H NMR, ^{13}C NMR spectra of all compounds are available.

References and notes

1. Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. J. Org. Chem. **1991**, *56*, 4971.
2. Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; Van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
3. (a) Nishimura, S.; Matsunaga, S.; Yoshida, M.; Hirota, H.; Yokoyama, S.; Fusetani, N. *Bioorg. Med. Chem.* **2005**, *13*, 449; (b) Nishimura, S.; Matsunaga, S.; Yoshida, M.; Nakao, Y.; Hirota, H.; Fusetani, N. *Bioorg. Med. Chem.* **2005**, *13*, 455.

4. (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385; (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335; (c) Liu, J. F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett*. **1998**, *39*, 1873; (d) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett*. **1998**, *39*, 9361; (e) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95; (f) Matsushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308; (g) Jung, M. E.; Karama, U.; Marquez, R. J. *Org. Chem.* **1999**, *64*, 663; (h) Matsushima, T.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780; (i) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249; (j) Zheng, B. Z.; Maeda, H.; Mori, M.; Kusaka, S. i.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, *J. Chem. Pharm. Bull.* **1999**, *47*, 1288; (k) Jung, M. E.; Marquez, R.*Tetrahedron Lett.* **1999**, *40*, 3129; (l) Matsushima, T.; Nakajima, N.; Zheng, B. Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855; (m) Zheng, B. Z.; Yamauchi, M.; Dei, H.; Kusaka, S. i.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441; (n) Zheng, B. Z.; Yamauchi, H.; Dei, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 1761; (o) Jung, M. E.; Marquez, R. *Org. Lett*. **2000**, *2*, 1669; (p) Jung, M. E.; Lee, C. P. *Org. Lett*. **2001**, *3*, 333; (q) Loh, T. P.; Feng, L. C. *Tetrahedron Lett*. **2001**, *42*, 6001; (r) Loh, T. P.; Feng, L. C. *Tetrahedron Lett.* **2001**, *42*, 3223; (s) Matsui, K.; Zheng, B. Z.; Kusaka, S. i.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. Eur. *J. Org. Chem.* **2001**, 3615; (t) Hearn, B. R.; Ciavarri, J. P.; Taylor, R. E. *Org. Lett.* **2002**, *4*, 2953; (u) Wong, C. M.; Loh, T. P. *Tetrahedron Lett*. **2006**, *47*, 4485; (v) Iqbal, J.; Nyavanandi, V. K.; Nanduri, S.; Vasudev, R.; Naidu, A. *Tetrahedron Lett*. **2006**, *47*, 6667.
5. (a) Smith, A. B. III; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *J. Am. Chem. Soc*. **2003**, *125*, 350; (b) Smith, A. B., III; Adams, C. M.; Barbosa, S. A. L.; Degnan, *P. Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042; (c) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc*. **2005**, *127*, 6186. (c) Dunetz, J. R.; Julian, L. D.; Newcom, J. S. and Roush, W. R. *J. Am. Chem. Soc*. **2008**, *130*, 16407-16416.
6. Yadav, J. S.; reddy, N. R. *Tetrahedron* **2010**, *66*, 3265-3274.
7. Yadav, J. S.; Rajender, V.; Rao, Y. G. *Org. Lett.* **2010**, *12*, 348-350.
8. Cooksey, J. P.; Ford, R.; Kocienski, P. J.; Pelotier, B.; Pons, J. M. *Tetrahedron* **2010**, *66*, 6462-6467.
9. Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013** *54*, 2022-2025
10. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Barry Sharpless, K. *Chem. Rev.* **1994**, *94*, 2483-2547; (b) Venkatesan, K.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2008**, *19*, 209-215. (c) Yadav, J. S.; Chinnam, V. V.; Krishna, B. B. M.; Rao, K. L. S.; Das, S. *Tetrahedron Lett*. **2015**, *56*, 1661-1663.
11. (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. (b) Pal, Zhenghong Peng, A.; Schuber Jr., P.l T.; Prasad, B. A. B.; Bornmann. W. G. *Tetrahedron Lett.* **2013**, *54*, 5555-5557.
12. Fu rstner, A.; Kattnig, E.; Olivier. *J. Am. Chem. Soc.* **2006**, *128*, 9194-9204.
13. Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu. I. *Tetrahedron Lett*, **1991**, *32*, 4937-4940.
14. Yadav, J. S.; Pattanayak, M. R.; Das, P. P.; Mohapatra, D. K. *Org. Lett*. **2011**, *13*, 1710-1713.
15. Norman, A. W.; Manchand, P. S.; Uskokovic, M. R.; Okamura, W. H.; Takeuchi, J.A.; Bishop, J. E.; Hisatake, J. I.; Koeffler, H. P.; Peleg, S. *J. Med. Chem.* **2000**, *43*, 2719-2730.
16. Narasimhulu, C. P.; Das, P. *Synthesis* **2009**, *3*, 474-482, 209.
17. (1) Crimmins. M. T.; and Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128-3129; (b) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810-13812
18. (a) Yadav, J. S.; Vardhan, V.; Das, S. *Synthesis* **2014**, 46, 2347-2352; (b) Sabitha, G.; Reddy, D. V.; Rao, A. S.; Yadav J. S. *Tetrahedron Lett.* **2010**, *51*, 4195-4198.
19. Jin, J.; Chen, Y.; Li, Y.; Wu, J. and Dai, Wei-Min. *Org. Lett.* **2007**, 9, 2585-2588.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Leave this area blank for abstract info.

Studies towards the total synthesis of (+)-13-deoxytedanolide: stereoselective synthesis of C1-C9 and C9-C17 fragments

Jhillu Singh Yadav,[*a] Vijaya Vardhan Chinnam,[a] and Saibal Das[a]

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India