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An aldol approach to the synthesis of the anti-tubercular agent erogorgiaene☆

J. S. Yadav,* A. K. Basak and P. Srihari

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A total synthesis of erogorgiaene is described in 16 steps. The synthesis relies upon a highly diastereoselective intramolecular Friedel–Crafts reaction of an oxetane derived via an asymmetric *syn* aldol coupling.

Erogorgiaene, isolated[1] along with other diterpenes from the West Indian sea whip *Pseudopterogorgia elisabethae*, displays promising anti-mycobacterial activity. Biological evaluation has revealed that it can inhibit 96% of *Mycobacterium tuberculosis* $H_{37}Rv$ growth at 12.5 μg/mL, making it an interesting lead in the synthesis of new anti-tubercular agents. Although erogorgiaene is not complex, the major challenge associated with its synthesis is control of the three stereocentres. Stereocontrol has been challenging due to the lack of functional groups near to the stereogenic centres (Fig. 1).

So far, two total syntheses and one formal synthesis of erogorgiaene have been reported. The first, by Hoveyda and co-workers,[2a] utilized catalytic asymmetric conjugate addition chemistry to install both the methyl stereogenic centres. The second, by Davies et al.,[2b] made use of an elegant carbene insertion/Cope rearrangement strategy to establish all of the stereocentres of the natural product. Harmata and Hong[2c] carried out a stereoselective intramolecular Michael addition of a chiral sulfoximine carbanion to an α,β-unsaturated ester to accomplish a formal synthesis. As part of our ongoing research programme of synthesizing biologically active natural products,[3] we herein report a total synthesis of erogorgiaene which relies upon an unprecedented, highly diastereoselective intramolecular Friedel–Crafts reaction of an oxetane derived via a non-Evans *syn* aldol coupling.

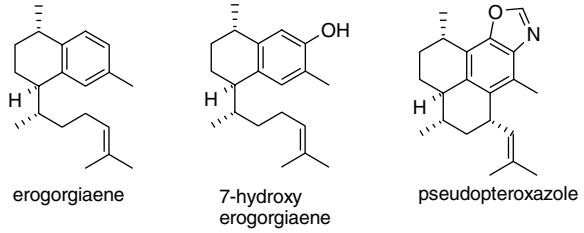

Figure 1. Diterpenes isolated from *Pseudopterogorgia elisabethae.*

The retrosynthesis of erogorgiaene is depicted in Figure 2. The synthesis began with introduction of the stereogenic centre at the benzylic position[4] using Evans' diastereoselective alkylation protocol. The lithiated Evans auxiliary **2**[5a] underwent coupling with readily available acid **1** under mixed anhydride conditions[5b] furnishing imide **3** in good yield (82%). Alkylation of the lithium enolate of **3**, generated by treatment with LDA in

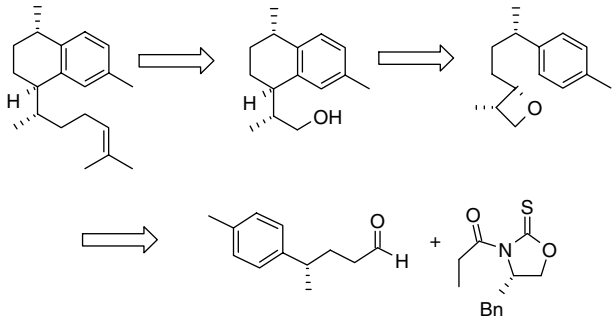

Figure 2. Retrosynthetic analysis of erogorgiaene.

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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: yadavpub@iict.res.in

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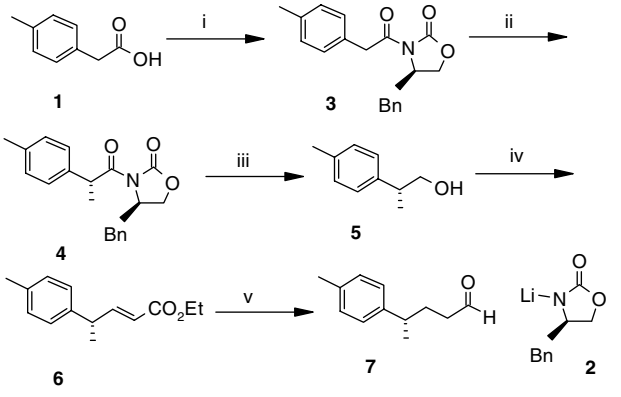
THF at −78 °C, with MeI afforded **4** with high diastereoselectivity[6] (>99%). The auxiliary in **4** was eliminated by reduction with $NaBH_4$ in THF/H_2O to give alcohol **5**.[7] Swern oxidation[8] of **5** and subsequent Wittig olefination led to the unsaturated ester **6** in good yield (86%). Reduction of the double bond with Pd/C, H_2 followed by treatment with DIBAL-H resulted in aldehyde **7** in 78% yield (Scheme 1).

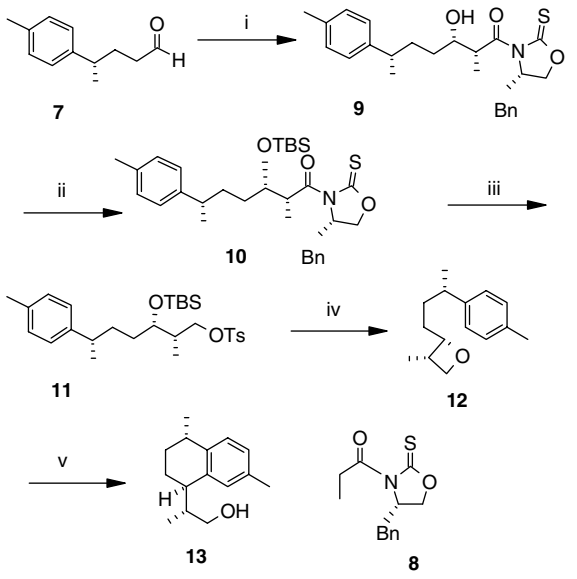
Aldehyde **7** underwent smooth aldol coupling with the titanium enolate of **8**[9] under Crimmins protocol[10] with high diastereoselectivity (49:1 dr) and yield (93%). The free hydroxy group in **9** was protected as its TBS ether with TBSOTf and 2,6-lutidine. Removal of the auxiliary in **10** by reduction[9] with $NaBH_4$ led to the corresponding alcohol, which was then tosylated with tosyl chloride and triethylamine in DCM. Tosylate **11** was first treated with a catalytic amount of PTSA in MeOH to deprotect the TBS ether and then with NaH in THF leading to oxetane **12** in excellent yield. The crucial intramolecular Friedel–Crafts reaction of oxetane **12** was carried out following the protocol[11a] generally employed for epoxides. As anticipated, the reaction proceeded smoothly, at ambient temperature, resulting in a single diastereomer[11b] **13** (Scheme 2).

At this stage all the stereogenic centres had been introduced. The next step was to attach the prenyl moiety to alcohol **13**. Alcohol **13** was converted to the corresponding iodide and then treated with prenyl magnesium bromide[12] following the conditions described in the literature.[13] Unfortunately, no reaction occurred. The corresponding bromide and tosylate also failed to undergo reaction with the prenyl Grignard. Hence, we oxidized alcohol **13** under Swern conditions[8] and subsequently carried out a Wittig olefination to obtain unsaturated ester **14**.

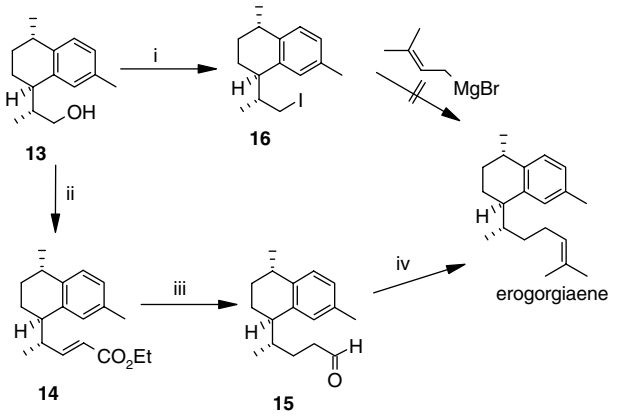
Saturation of the double bond with Pd/C, H_2 and then reduction of the ester with DIBAL-H furnished aldehyde **15** in 82% yield. The aldehyde was then treated with isopropyltriphenylphosphorane in THF to give erogorgiaene in 80% yield (Scheme 3). The synthetic



Scheme 1. Reagents and conditions: (i) PivCl, Et_3N, THF, **2**, −20 °C to rt, 4 h, 82%; (ii) LDA, MeI, −78 °C to −30 °C, 3 h, 56%; (iii) $NaBH_4$, THF/H_2O, rt, 12 h, 95%; (iv) (a) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C; (b) Ph_3PCHCO_2Et, rt, 12 h, 86%; (v) (a) Pd/C, H_2, EtOAc; (b) DIBAL-H, DCM, −78 °C, 30 min, 78%.



Scheme 2. Reagents and conditions: (i) **8**, $TiCl_4$, $^iPr_2NEt$, −78 °C, 1.5 h, 93%; (ii) TBSOTf, 2,6-lutidine, DCM, 0 °C, 30 min, 97%; (iii) (a) $NaBH_4$, MeOH, rt, 12 h, 78%; (b) TsCl, Et_3N, DCM, rt, 3 h, 97%; (iv) PTSA, MeOH then NaH, THF, rt, 12 h, 93%; (v) $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 3 h, 81%.



Scheme 3. Reagents and conditions: (i) Ph_3P, I_2, ImH, toluene, rt, 1 h, 84%; (ii) (a) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C; (b) Ph_3PCHCO_2Et, rt, 12 h, 84%; (iii) (a) Pd/C, H_2, EtOAc; (b) DIBAL-H, DCM, −78 °C, 30 min, 82%; (iv) $Me_2CHPPh_3{}^+I^-$, *n*-BuLi, THF, 0 °C, 3 h, 80%.

compound[14] was found to be identical with the natural compound based on comparison of ^1H NMR, ^{13}C NMR and MS spectra and optical rotation.[1]

In summary, we have accomplished a linear synthesis of erogorgiaene in an efficient and highly stereocontrolled fashion requiring 16 steps with an overall yield of 8.2%. The strategy is quite versatile and can be applied to the synthesis of all the possible stereoisomers of erogorgiaene.

Acknowledgement

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Supplementary data

Experimental details, spectral data and copies of ^{1}H NMR and ^{13}C NMR spectra of selected compounds are available in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.103.

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14. Data for compound **9**: Oil, $[\alpha]_D^{25}$ +75.6 (*c* 1.1, $CHCl_3$); IR (KBr, neat) *v* 3451, 2925, 2868, 1694, 1453, 1370, 1190, 956, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, 3H, $J = 6.8$ Hz), 1.24 (d, 3H, $J = 6.8$ Hz), 1.41–1.64 (m, 2H), 1.73–1.89 (m, 1H), 2.25 (s, 3H), 2.47 (d, 1H, $J = 3.0$ Hz), 2.58–2.69 (m, 2H), 3.21 (dd, 1H, $J = 3.0$, 12.8 Hz), 3.89–4.01 (m, 1H), 4.30–4.31 (m, 2H), 4.45–4.75 (m, 1H), 4.82–4.94 (m, 1H), 7.01–7.05 (m, 4H), 7.16–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.23, 20.79, 22.68, 32.19, 34.43, 37.58, 39.47, 41.93, 59.88, 70.06, 71.78, 126.70, 127.32, 128.90, 128.96, 129.25, 135.11, 135.18, 144.06, 177.89, 185.05; MS–ESIMS *m/z* 448 (M+Na)$^+$; HRMS calcd for $C_{25}H_{31}NO_3NaS$: 448.1922, found 448.1933.

    Compound **12**: colourless liquid, $[\alpha]_D^{25}$ +40.4 (*c* 3.8, $CHCl_3$); IR (KBr, neat) *v* 2960, 2927, 2865, 1513, 1456, 1380, 937, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (d, 3H, $J = 7.5$ Hz), 1.23 (d, 3H, $J = 7.5$ Hz), 1.28–1.40 (m, 2H), 1.54–1.70 (m, 2H), 2.31 (s, 3H), 2.48–2.69 (m, 1H), 2.81–2.99 (m, 1H), 3.97 (t, 1H, $J = 6.0$ Hz), 4.62–4.72 (m, 2H), 7.00 (d, 2H, $J = 9.0$ Hz), 7.04 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 20.9, 22.5, 30.1, 31.9, 33.4, 39.7, 75.5, 85.1, 126.8, 129.0, 135.2, 144.3; MS–ESIMS *m/z* 241 (M+Na)$^+$; HRMS calcd for $C_{15}H_{22}ONa$: 241.1568 found 241.1560.

    Erogorgiaene: colourless liquid, $[\alpha]_D^{27}$ +23.2 (*c* 0.75, $CHCl_3$); Ref. 1 $[\alpha]_D^{25}$ +24.4 (*c* 3.2, $CHCl_3$), Ref. 2b $[\alpha]_D^{25}$ +21.4 (*c* 0.14, $CHCl_3$), Ref. 2a $[\alpha]_D^{20}$ +40.6 (*c* 0.14 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.63 (d, 3H, $J = 6.6$ Hz), 1.26 (d, 3H, $J = 7.3$ Hz), 1.30–1.38 (m, 2H), 1.39–1.48 (m, 1H), 1.49–1.56 (m, 1H), 1.62 (br s, 3H), 1.70 (br s, 3H), 1.76–1.83 (m, 1H), 1.87–1.93 (m, 1H), 1.99–2.14 (m,3H), 2.28 (s, 3H), 2.64–2.77 (m, 1H), 2.82–2.88 (m, 1H), 5.12 (br t, 1H, $J = 6.6$ Hz), 6.86 (d, 1H, $J = 8.0$ Hz), 6.94 (s, 1H), 7.06 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 17.7, 21.1, 21.5, 21.8, 25.7, 26.3, 31.8, 32.8, 35.2, 37.0, 41.5, 124.9, 126.0, 126.4, 128.1, 131.2, 134.7, 139.9, 140.4; MS–LCMS *m/z* 270 (M^+). The spectroscopic data are consistent with previously reported data.[1,2a,b]