Synthetic studies towards the novel diterpenoid rameswaralide: RCM mediated acquisition of the tricyclic core

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Abstract—A synthetic approach towards the novel anti-inflammatory diterpenoid rameswaralide from the cis-Corey lactone involving a tandem RCM and Diels–Alder reaction has been conceived and endeavors so far have led to the acquisition of the BCD ring fragment of the natural product.

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In 1998, collaborative efforts between the research groups of Venkateswarlu and Faulkner led to the isolation of a novel diterpenoid, rameswaralide 1, from the soft coral Sinularia dissecta collected from the Mandapam coast two years earlier.1 The stereostructure of 1 was determined through recourse to incisive 2D NMR techniques and chemical transformation to dihydrorameswaralide 2 to reveal the presence of the unusually stable enol moiety.1 The unique framework of rameswaralide 1 has close biosynthetic kinship with the diterpenoids mandapamate 3 and isomandapamate 4 with which it co-occurs in the same soft coral species.2 The tetracyclic framework of rameswaralide 1, composed of a 5,7,6-fused tricarbocyclic core and functionalities spread in all its rings and embellished with six stereogenic centres is a challenging synthetic target in its own right. However, it is the observation of promising anti-inflammatory activity3 associated with 1 and its derivatives, with inhibitory activity against TNF-α, IL-15, IL-5 and Cox2 with an IC50 in 0.5–5 µg/mL concentration3 that has added special attraction to its synthetic pursuit. Although a total synthesis of 1 has not been achieved so far, a related model study4 has recently surfaced in the literature. As part of our continuing interest in the total synthesis of diterpenoids with 5,7,6-fused tricarbocyclic frameworks,5 we disclose in this letter a synthetic approach to 1 that has so far culminated in the acquisition of the BCD tricyclic core present in the natural product.

Our synthetic strategy towards 1 evolved around the retrosynthetic theme is depicted in Scheme 1. It was envisaged that the cis-fused six-membered ring A could be appended to the preformed tricyclic BCD core 5 through [4+2]-cycloaddition protocols on the enone moiety. Thermal and Lewis acid catalyzed Diels–Alder reactions to cycloheptenones are well precedented6 and in the case of 5 an examination of models revealed that the cycloaddition was expected to be face selective with the diene approaching from the α-face to deliver the desired C5,C14 ring junction stereochemistry. The key cycloheptenone moiety in 5 was sought to be generated.
through a RCM reaction in 6 which, in turn, could be elaborated from the all cis-Corey lactone 7 (Scheme 1). The choice of the all cis-Corey lactone 7 as the launch pad was crucial as it embodies the CD rings of the natural product 1 and the required stereochemistry at C7, C10 and C11 is embedded into it. Therefore, our initial objective was to devise a convenient access to 7 in an appropriately protected form for further elaboration. Several syntheses of the all cis-Corey lactone, emanating from diverse starting materials, have been recorded in the literature, particularly in the context of accessing iso-prostanes and related prostaglandin analogues. However, our present endeavors warranted development of a de novo synthesis of 7 that became our initial objective. Towards this end, the recently reported and readily available 7-keto-norbornene derivative 8 was selected as the starting material. Wittig methoxymethylation in 8 led to enol ether 9 and carefully controlled acid catalyzed hydrolysis (<0 °C) in 9 to the intermediate aldehyde 10 followed by immediate borohydride reduction led to a readily separable mixture (4:1) of the syn-11 and anti-12 alcohols in good yield (Scheme 2). Protection of the hydroxyl group in 11 as its TBS derivative followed by acetate hydrolysis and TPAP oxidation furnished the syn-norbornene derivative 13.9 Baeyer–Villiger oxidation of 13 presented some initial chemoselectivity problems (Scheme 3) because of the steric shielding of the C2 carbonyl group by the C7 syn substituent but high chemoselectivity was secured by carrying out the reaction in basic H2O2 to obtain lactone 15 with the complete exclusion of the epoxide product 14. Reconstructive iodolactonization of 15 furnished iodolactone 16 in good yield, however, we were surprised to find that the lactone protection was lost during the process (Scheme 3). The two hydroxyl groups in 16 were protected as the TES derivative 17 and reductive deiodination furnished the all cis-Corey lactone derivative 18 (Scheme 3).9 Although the route to 18 was somewhat long, its execution was straightforward and this key intermediate could be routinely obtained in gram quantities.

The next task was to set up the RCM reaction to generate the seven-membered B ring of rameswaralide 1. In this context, lactone 18 was stereoselectively allylated to yield 19 with the addition exclusively from the convex face (Scheme 4).9 Selective deprotection of the primary hydroxyl group in 19 led to 20 and further PDC oxidation furnished the sensitive endo-aldehyde 21 (Scheme 4). Addition of vinylmagnesium bromide to 21 gave the diastereomeric mixture 22 and was as such oxidized with PDC to enone 239 required for effecting the key RCM reaction. Exposure of 23 to the Grubbs’ second generation catalyst11 resulted in smooth generation of the desired cycloheptenone moiety and formation of 24.9 The stereostructure of 24 was secured through an X-ray crystal structure determination.12

With the availability of the advanced BCD ring intermediate 24, its Diels–Alder reactions with several dienes (1,3-butadiene, isoprene, furan, etc.) were attempted to append the A ring for which the literature precedent

Scheme 1. Retrosynthetic strategy.

Scheme 2. Reagents and conditions: (a) CH3OCH2PPh3Cl, KO/Am, THF, 0 °C, 2 h, 80%; (b) HClO4 (cat.), DCM, 0 °C, 2 h, 93%; (c) NaBH4, MeOH, 0 °C, 1 h, quant.; (11:12 = 4:1; (d) (i) TBSCI, imidazole, DCM, rt, 1 h, 96%; (ii) K2CO3, MeOH, 10 h, 92%; (c) TPAP, NMMO, rt, DCM, 3 h, 94%.

Scheme 3. Reagents and conditions: (a) mCPBA, NaHCO3/PTSA, 0 °C to rt, 2 h, 89%; (b) H2O2, NaOH, MeOH, 0 °C, 2 h, 95%; (c) CF3COOH, K2CO3, MeOH, 0 °C, 1 h, 95%; (d) (i) NaOH, MeOH, rt, 12 h; (ii) KI, I2, H2O, rt, 3 h, 86% (two steps); (e) TESCl, Py, rt, 12 h, 90%; (f) (°Bu)3SnH, AIBN, C6H6, Θ, 2 h, 95%.

Scheme 4. Reagents and conditions: a) mCPBA, NaHCO3/PTSA, 0 °C to rt, 2 h, 89%; (b) H2O2, NaOH, MeOH, 0 °C, 2 h, 95%; (c) CF3COOH, K2CO3, DCM, 0 °C, 1 h, 95%; (d) (i) NaOH, MeOH, rt, 12 h; (ii) KI, I2, H2O, rt, 3 h, 86% (two steps); (e) TESCl, Py, rt, 12 h, 90%; (f) (°Bu)3SnH, AIBN, C6H6, Δ, 2 h, 95%.
exists. However, despite several such attempts under different thermal and catalyzed regimes, success eluded us and this forced us to explore an alternative approach although not successfully. The alternative procedure that we sought to append ring A was through an enyne metathesis in a precursor such as to furnish the diene which was expected to be more amenable to Diels–Alder reaction to deliver ring A as in (Scheme 5).

Consequently, the TES protected cis-Corey lactone was propargylated to give (Scheme 6). Selective deprotection of the primary hydroxyl group and PDC oxidation led to aldehyde (ii) PDC, DCM, 0 °C, 3 h, 88% (no column chromatography); (c) H2C=CHMgBr, THF, –78 °C, 30 min, 64%; (d) PDC, DCM, 0 °C, 4 h, 80%; (e) Grubbs’ I/II gen. catalyst, DCM/benzene/toluene, rt/reflux.

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References and notes


6.5 Hz), 2.05–1.99 (1H, m), 1.98 (3H, s, OCOCH 3), 1.04

2.71 (1H, dd, J = 12.9, 4.8, 3.8 Hz), 6.09 (1H, d1/2Aq, J = 12.9, 3.7 Hz), 5.07 (1H, t, J = 7.5 Hz), 4.82 (1H, t, J = 6.8 Hz), 4.13 (1H, dt, J = 12, 3.7 Hz), 3.04–2.91 (3H, m), 2.42–2.29 (2H, m), 2.11 (1H, d1/2Aq, J = 15, 1.8 Hz), 0.90 (9H, s, 3 × CH 3), 0.56 (6H, s, 3 × CH 2). 13C NMR (75 MHz, CDCl 3 ); δ 178.0, 84.6, 73.5, 59.7 (CH 3 ), 50.54, 38.4, 30.4 (CH 2 ), 6.7 (3 × CH 3), 6.6 (3 × CH 3), 4.6 (3 × CH 2), 4.3 (3 × CH 3). HRMS (ES): m/z Calculated for C 12 H 20 O 4 Si 2: 628.1229, found: 628.1227. Compound 29: IR (neat): ν max 1678, 1698 cm −1. 1H NMR (300 MHz, CDCl 3 ): δ 6.58 (1H, d1/2Aq, J = 17.4, 10.2 Hz), 6.31 (1H, d1/2Aq, J = 17.4 Hz), 5.87–5.74 (1H, m), 5.76 (1H, d, J = 10.2 Hz), 5.20–5.09 (2H, m), 4.92 (1H, t, J = 6.9 Hz), 4.77 (1H, br s), 3.35–3.31 (1H, m), 3.07–3.01 (2H, m), 2.67–2.63 (2H, m), 2.19 (1H, d1/2Aq, J = 15 Hz), 1.98 (1H, d1/2Aq, J = 15, 6.9, 3.6 Hz), 0.99–0.83 (9H, m, 3 × CH 3), 0.62–0.52 (6H, m, 3 × CH 2). 13C NMR (75 MHz, CDCl 3 ); δ 196.8, 179.7, 134.7, 134.3, 128.1 (CH 2), 118.5 (CH 2), 81.7, 74.4, 59.9, 43.2, 43.1, 42.5 (CH 2), 36.6 (3 × CH 3), 4.6 (2 × CH 2). HRMS (ES): m/z Calculated for C 10 H 14 O 3 Si: 373.1811 [M + Na] +, found: 373.1801. Compound 24: Mp 99–100 °C. IR (KBr) ν max 1786, 1662 cm −1. 1H NMR (300 MHz, CDCl 3 ); δ 6.45 (1H, d1/2Aq, J = 12.9, 4.8, 3.8 Hz), 6.09 (1H, d1/2Aq, J = 12.9, 3.7 Hz), 5.07 (1H, t, J = 7.5 Hz), 4.82 (1H, t, J = 6.8 Hz), 4.13 (1H, dt, J = 12, 3.7 Hz), 3.04–2.91 (3H, m), 2.42–2.29 (2H, m), 2.11 (1H, d1/2Aq, J = 15, 1.8 Hz), 0.90 (9H, s, 3 × CH 3), 0.56 (6H, s, 3 × CH 2). 13C NMR (75 MHz, CDCl 3 ); δ 198.6, 177.4, 142.3, 143.4, 82.0, 75.8, 58.7, 45.3, 42.2, 42.0 (CH 2), 32.7 (CH 2), 6.6 (3 × CH 3), 4.5 (3 × CH 3). HRMS (ES): m/z Calculated for C 20 H 40 O 4 Si: 454.1948 [M + Na] +, found: 454.1941. Compound 29: IR (neat): ν max 2729, 1767, 1723 cm −1. 1H NMR (300 MHz, CDCl 3 ); δ 9.85 (1H, s, −CHO), 5.06 (1H, t, J = 7.5 Hz), 4.87 (1H, t, J = 3.3 Hz), 3.33 (1H, dt, J = 8.1, 5.4 Hz), 3.16 (1H, q, J = 5.1 Hz), 2.89–2.72 (3H, m), 2.22 (1H, d1/2Aq, J = 15.3 Hz), 2.05–1.94 (2H, m), 0.95–0.90 (9H, m, 3 × CH 3), 0.63–0.55 (6H, m, 3 × CH 2). 13C NMR (75 MHz, CDCl 3 ); δ 200.2, 178.1, 82.6, 80.4, 73.9, 70.7, 61.0, 43.0, 42.8, 42.1 (CH 2), 21.7 (CH 2), 6.6 (3 × CH 3), 4.5 (3 × CH 3).


12. X-ray data for 24: C 27 H 20 O 4 Si, M 0 = 322.3, colourless crystal, crystal system: orthorhombic, space group: Pnma2 1, cell parameters a = 21.6885 (87) A , b = 7.8197 (31) A , c = 10.6843 (43) A , V = 1812.03 (13) A 3, Z = 4, p calc = 1.86 g cm −3, F(000) = 650.9, μ = 0.144 mm −1. Total no of ls: parameters: 202, R 1 = 0.098 for 1702 reflections with Fo > 4σ(Fo) and 0.156 for all 2792 reflections, wR 2 = 0.239, GOF = 1.060, restrained GOF = 1.060 for all data (CCDC 281711).
