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Towards the synthesis of prevezol C: total enantioselective synthesis of (−)-2-*epi*-prevezol C

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ABSTRACT

(−)-2-*epi*-Prevezol C was readily accessed from the chirons (−)- and (+)-limonene oxide in a total of nine steps and in 24% yield. This efficient enantioselective synthesis of this complex product utilises a highly stereoconvergent, substrate-controlled allylic alkylation strategy to assemble rapidly the unprecedented diterpene core.

A family of novel cytotoxic-brominated diterpenes, prevezols B–E, was isolated from the organic extracts of the red alga *Laurencia obtusa* (Fig. 1).[1] Elucidation of their structures and relative stereochemistry, by comprehensive spectral data analyses, revealed a family of *syn*-bromohydrins with carbon skeletons that were unprecedented in the literature. The structure of prevezol A had been previously established, and the discovery of metabolites C–E allowed revision of the earlier proposed structure of prevezol B.[2]

Whilst modern spectroscopic techniques have advanced in recent years, regio and stereoselective synthesis still remains a requirement for the confirmation of structure and determination of absolute stereochemistry. This has been highlighted recently in an excellent review by Nicolaou and Snyder regarding the misassignment of natural products[3] and in an article by Burton and co-workers, which reassessed the structures of elatenyne and chloroenyne natural products extracted from *Laurencia majuscula*.[4] As the first step in the synthesis of these complex natural products we investigated strategies for the synthesis of prevezol C (Fig. 1), to explore routes for the formation of this unique carbon skeleton and to confirm the reported structure of the Western hemisphere (ring B).

The relative stereochemistry of the Eastern hemisphere (ring A) of prevezol C was assigned due to spectral agreement with the values reported for prevezol A,[1,2] which was identified by comparison of the ^{13}C NMR data of obtusadiol and rogioldiol A (Fig. 2).[2,5] The relative stereochemistry of the Western hemisphere (ring B) of prevezol C was assigned based on NOESY correlations. Thus, before synthesis of the challenging *syn*-bromohydrin moiety commenced we needed to develop methodology to connect the Eastern and Western hemispheres of prevezol C and to develop strategies for constructing and confirming the required stereochemistry in the Western hemisphere. Thus, as a prelude to the harder problem, we synthesised the easier *trans*-bromohydrin of prevezol C [(−)-*epi*-prevezol C **1**], epimeric at the 2-position (Fig. 2).

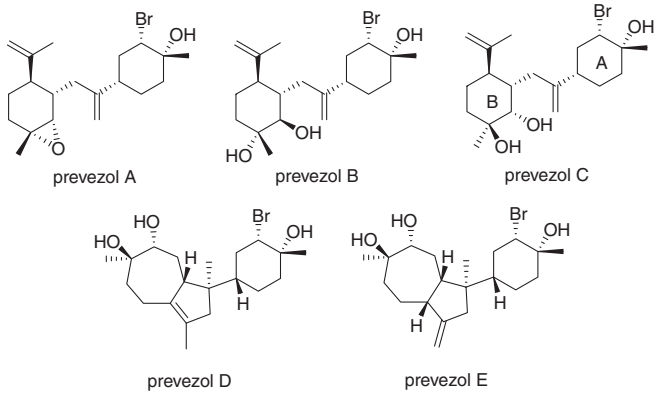

Figure 1. The structures of prevezols A–E.

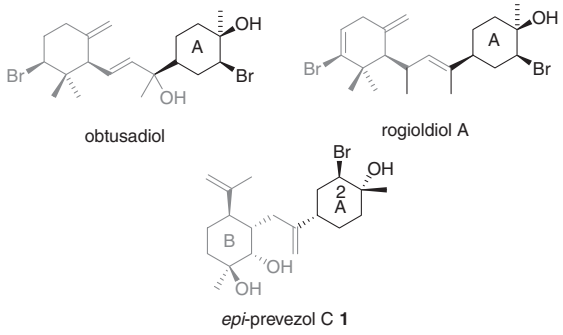

Figure 2. The structures of obtusadiol, rogioldiol A and *epi*-prevezol C (**1**).

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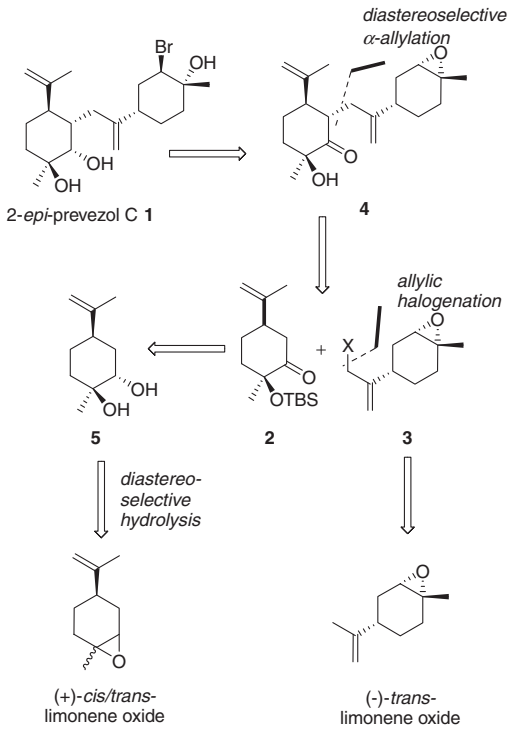
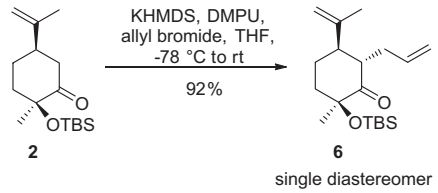
Due to the structural homology shared by the two hemispheres of *epi*-prevezol C (**1**) we envisaged a stereoconvergent synthetic approach utilising limonene oxide (Scheme 1). The key disconnection in the retrosynthesis is a diastereoselective carbon–carbon bond-forming alkylation reaction of the ketone **2** and the allylic halide **3**. It was anticipated that the alkylated product **4** would form diastereoselectively as a result of the isoprenyl substituent preferentially residing in the equatorial position, thereby controlling the stereochemical course of the reaction. However if this is not the case, epimerisation of the *syn*-isomer to the thermodynamically stable *anti*-isomer **4** should be facile. Recent efforts in our laboratories have focused on accessing the *trans*-diaxial and *trans*-diequatorial diols of limonene oxide, which are derived from a commercially available diastereomeric mixture of *cis* and *trans* isomers, in high yields and diastereoselectivities.[6] We hoped to employ the *trans*-diaxial diol **5** in the total synthesis of (−)-*epi*-prevezol C (**1**). It was also anticipated that the required allylic halide **3** could be readily synthesised from (−)-*trans*-limonene oxide via an allylic halogenation reaction.

The required *tert*-butyldimethylsilyloxy-ketone **2** was synthesised according to our published procedure.[7] Standard allylic alkylation conditions of the lithium enolate of the silyloxy ketone **2**, formed at −78 °C with LDA,[8] with allyl bromide gave poor yields. Employing a modified version of the conditions reported by Palomo et al.,[9] which used an excess of KHMDS in the presence of 20% v/v DMPU (Scheme 2), gratifyingly afforded the allylated species **6** in excellent conversion and as a single diastereomer, as determined by analysis of its ^{1}H NMR spectrum.

The stereochemistry at the α-carbon of the allylated product **6** was elucidated to be the thermodynamic *trans* product via analysis of the COSY and NOESY spectra. The coupling constants (J = 11.8, 9.5 and 2.5 Hz) of the proton adjacent to the carbonyl group were also consistent with the proton existing in the axial position. The reaction of the allylated product **6** with 5% NaOMe (5 days) showed no change in its ^{1}H NMR spectrum, which is consistent with an equatorial allyl chain. It is postulated that excellent diastereofacial



Scheme 1. Retrosynthesis of *epi*-prevezol C **1**.



Scheme 2. Synthesis of the model alkylated product **6**.

control was obtained due to the 1,3-diaxial interaction encountered by the incoming electrophile with the axial TBS group, and thereby alkylating in a twist-boat conformation,[10] and not due to base-catalysed epimerisation of an axially alkylated intermediate (Fig. 3). Furthermore, quenching the reaction at −40 °C with saturated ammonium chloride afforded the equatorial product, exclusively.

Given the positive outcome of the model alkylation studies, we next focused our attention on the synthesis of the key electrophile, 10-halo-*trans*-limonene oxide **3**. Preparation of the allylic halide **3**, by halogenation of *trans*-limonene oxide was not trivial; traditional Wohl–Ziegler conditions (NBS, CCl_4, AIBN or dibenzoylperoxide),[11] and derivatives thereof (NBS, AcOH)[12] gave complex mixtures. However, optimisation of Moreno-Dorado's conditions,[13] utilising a stoichiometric quantity of iodometrically titrated sodium hypochlorite,[14] in the presence of either $CeCl_3$ (1.1 equiv) or $InCl_3$ (1.1 equiv),[15] in a binary solvent system (1:1 CH_2Cl_2/H_2O) afforded the allylic chloride **3a** in high yield (Scheme 3). Minimal amounts of the bis-chloro by-product were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Recently, Jastrzebska et al. demonstrated that the π-allyl complex derived from an allylic chloride[16] could be used as an alternative to the more routinely employed allylic acetate and carbonate electrophiles.[17] Unfortunately, application of these conditions to our allylic chloride **3a** proved unsuccessful. The conditions for the model alkylation, KHMDS/DMPU (2.2 equiv/20% v/v), also did not result in the alkylated product **4a**. Pleasingly, conversion of the allylic chloride **3a** into the corresponding more reactive iodo species **3b** yielded an extremely reactive electrophile which participated easily in an allylic alkylation reaction with the enolate derived from ketone **2**, even in the absence of DMPU (Scheme 3).[18] Like the model studies, the diterpene oxide **4a** was also observed to be a single diastereomer by ^{1}H NMR spectroscopic analysis. The treatment of the diterpene oxide **4a** with TBAF (1.5 equiv) in refluxing THF readily cleaved the *tert*-butyldimethylsilyl group to give **4b**

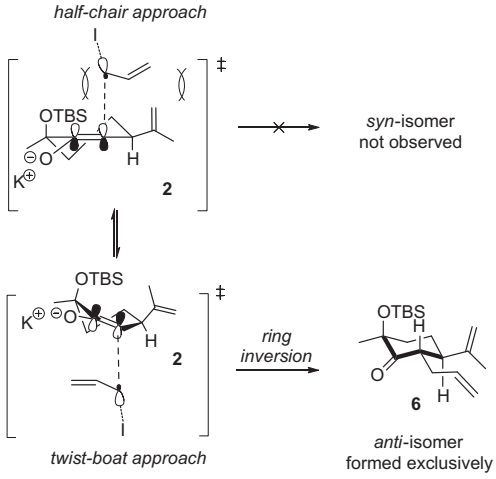
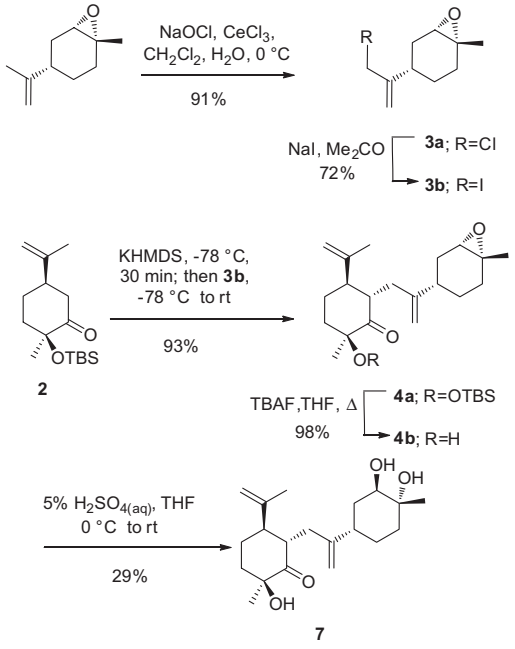


Figure 3. The diastereomorphic transition states for substrate control to form the desired allylated ketone **6**.



Scheme 3. Synthesis of the key intermediate oxide **4b**.

with a single diastereomer observed by ^{1}H NMR spectroscopic analysis (Scheme 3). As a final confirmation of the absolute stereochemistry of the diterpene core, **4b** was reacted under acidic conditions to give the corresponding triol **7**. An X-ray crystal structure of the triol **7** confirmed that the alkylation reaction had occurred to give the depicted stereochemistry (Fig. 4).[19,20]

Formation of the required *trans*-diol **8**, the penultimate compound, occurred exclusively via a chelation-controlled stereoselective ketone reduction employing sodium triacetoxyborohydride in acetic acid/acetonitrile at −40 °C (Scheme 4).[21,22] A regiospecific acid-catalysed nucleophilic oxirane opening was achieved with LiBr/AcOH in cold THF,[23] to afford the 2-bromo-epimer of prevezol C (**1**) in 64% yield.[24]

Comparison of the ^{13}C NMR spectroscopy resonances of 2-*epi*-prevezol C (**1**) with prevezol C showed excellent correlation, with the expected exceptions of the resonances of the epimeric carbon, C2, and its neighbours (Supplementary data). In the Western hemisphere the resonances of the stereogenic centres C9, C10, C13 and C14 closely corresponded with those reported for prevezol C (<0.6 ppm difference, Figure 5 and Supplementary data). This leads us to believe that the relative stereochemistry of the Western hemisphere has been correctly assigned in the natural product.

In conclusion we have synthesised (−)-2-*epi*-prevezol C (**1**) in nine steps and 24% overall yield from (−)-*trans*-limonene oxide and (+)-*cis*/*trans*-limonene. This work represents the first total synthesis of a prevezol analogue and the synthetic construction of their unique carbocyclic framework.

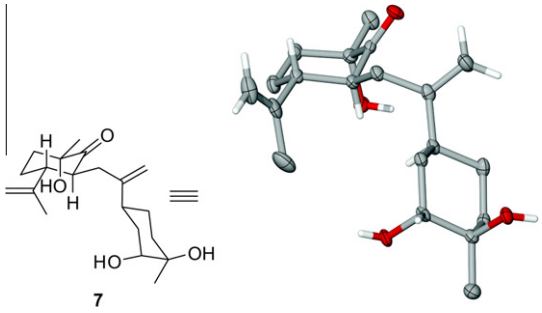
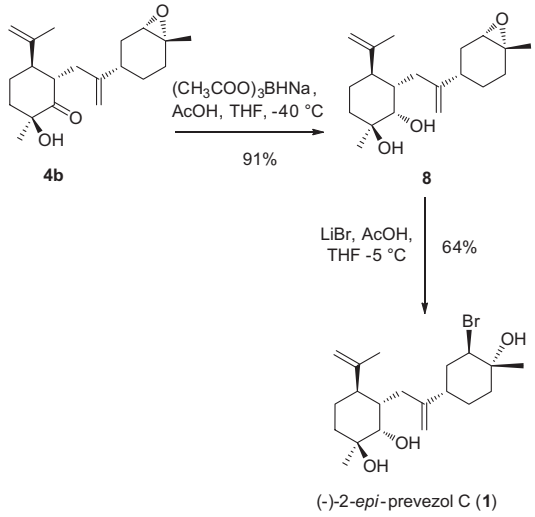


Figure 4. The X-ray crystal structure of triol **7**.



Scheme 4. Synthesis of *epi*-prevezol C (**1**).

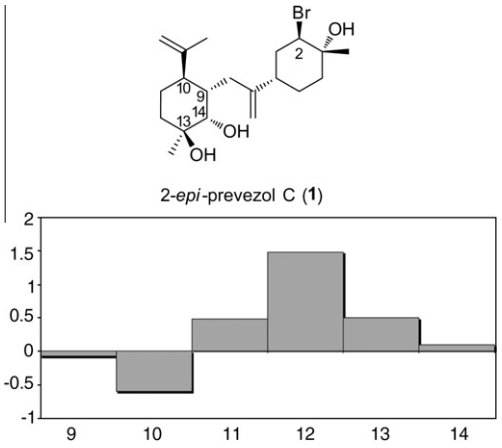


Figure 5. Comparison of the ^{13}C NMR signals of the Western hemisphere of prevezol C and 2-*epi*-prevezol C (**1**). Horizontal and vertical axes show carbon number and $\Delta\delta$ values. The numbering of the rings is consistent with that used by Iliopoulou et al.[1]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.019.

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18. *(2S,5R,6S)-2-(tert-Butyldimethylsilyloxy)-2-methyl-6-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)allyl)-5-(prop-1-en-2-yl) cyclohexanone* (**4a**): KHMDS (0.5 M solution in toluene; 14.10 mL, 7.05 mmol) was added slowly to a stirred solution of the ketone **2** (1.66 g, 5.88 mmol) in THF (35 mL) at −78 °C, under an inert atmosphere. After 30 min, a solution of the allylic iodide **3b** (1.82 g, 6.54 mmol) in THF (35 mL) was added slowly. The mixture was warmed to an ambient temperature, stirred for 12 h and then the reaction was quenched with cold saturated $NH_4Cl_{(aq)}$ (75 mL). The mixture was extracted with Et_2O (100 mL); the organic fraction was washed with brine (100 mL), dried over ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (20:1 hexanes/EtOAc) afforded the title compound as a colourless oil (2.37 g, 93%). $[\alpha]_D^{20}$ −8.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz) δ 0.03 (s, 3H), 0.147 (s, 3H), 0.94 (s, 9H), 1.30 (s, 3H), 1.31 (s, 3H), 1.42–1.48 (m, 3H) 1.61–1.67 (m, 2H), 1.71 (s, 3H) 1.77–1.87 (m, 3H), 1.99–2.08 (m, 4H), 2.15–2.21 (m, 1H), 2.28 (dd, *J* = 15.9, 10.8 Hz, 1H), 2.97 (d, *J* = 5.5 Hz, 1H), 3.39–3.43 (m, 1H), 4.57 (s, 1H), 4.66 (s, 1H), 4.73 (s, 1H), 4.79 (t, *J* = 1.5 Hz, 1H). ^{13}C NMR (125 MHz) δ −2.3, 1.8, 18.4, 23.3, 24.0, 24.8, 26.1, 26.8, 30.5, 30.6, 31.2, 40.2, 42.1, 46.7, 55.1, 57.7, 59.6, 78.8, 107.4, 112.8, 146.3, 152.3, 212.3. IR (film): 3076 (w), 2932 (br s), 2858 (m), 1720 (s), 1644 (s), 1472 (m) 1448 (m), 1376 (m), 1254 (s), 1210 (w), 1170 (m), 1132 (m), 1095 (m), 1050 (m), 1005 (m), 956 (m), 861 (m), 835 (s). HRMS (ESI) calcd for $C_{26}H_{44}NaO_3Si$ $(M+Na)^+$ 455.2957; found 455.2957.
19. The X-ray crystal data of **7**·H_2O (CCDC-776506) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
20. All attempts to convert the secondary alcohol into the corresponding bromide with inversion of configuration were unsuccessful.
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22. With $NaBH_4$/MeOH (−5 °C; 5 min) a 5:1 (*trans*/*cis*) mixture of diols was obtained (determined by ^{1}H NMR spectroscopic analysis).
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24. *(−)-2-epi-Prevezol C* (**1**): LiBr (72 mg, 829 μmol) in anhydrous THF (2 mL) was introduced through a rubber septum, via the aid of a syringe, to a solution of diterpene diol **8** (49 mg, 152.9 μmol) in THF (1.5 mL) and AcOH (28.4 μL, 458.7 μmol) at 0 °C under an inert atmosphere. The reaction mixture was allowed to warm at an ambient temperature, and the reaction was deemed complete after 2 h via TLC analysis (1:1 EtOAc/hexanes). The reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ (5 mL), partitioned with Et_2O (15 mL), washed with saturated brine (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded the title compound as a colourless oil (39 mg, 64%). $[\alpha]_D^{20}$ −18.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz) δ 1.41 (s, 3H), 1.45–1.49 (m, 2H), 1.56–1.69 (m, 6H) 1.69 (s, 3H), 1.72–1.79 (m, 3H), 1.89 (m, 8H) 2.16 (d, *J* = 14.5 Hz, 1H), 2.39–2.47 (m, 1H), 3.36 (s, 1H), 4.14–4.16 (m, 1H), 4.74–4.78 (m, 2H), 4.85 (s, 1H), 4.87 (s, 1H). ^{13}C NMR (125 MHz) δ 18.9, 26.0, 27.1, 28.4, 29.8, 33.1, 33.3, 35.3, 35.6, 36.2, 36.9, 44.3, 60.2, 71.79, 71.84, 73.7, 110.4, 111.9, 148.1, 151.0. IR (film): 3424 (br s), 3072 (w), 2928 (s), 2857 (m), 1702 (w), 1640 (m), 1451 (m), 1376 (m), 1260 (m), 1180 (m), 1099 (m), 1030 (m), 924 (w), 891 (m), 798 (m), 759 (m). HRMS (ESI) calcd for $C_{20}H_{32}BrO_3$ $(M-H)^-$ 399.1535; found 399.1536.