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Total Synthesis of Crotomachlin

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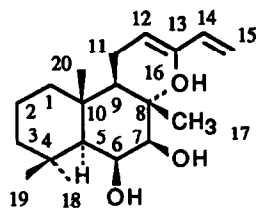
Abstract- The synthesis of the racemic 6β, 7β, 8α-trihydroxy labdadiene, 1 was achieved starting from decalin 3. Diene 1 was found to be identical to crotomachlin, a diterpene from Croton macrostachys. in which the configuration at C-8 has not been established with certainty.

In a previous paper,[1] we described the reactions required to introduce a diene side chain and hydroxyl substituents on a substituted decalin prepared from geraniol and β-ionone. We now report the first total synthesis of racemic diene 1, thereby establishing the complete stereochemistry of the diterpene crotomachlin product isolated from *Croton macrostachys*[2] found to be identical with 6β,7β-dihydroxy-12E-abienol isolated by Bohlmann and *al.*[3] from *Koanophyllon conglobatum.*[4] This compound shows antilipoxygenase activity *in vitro.*

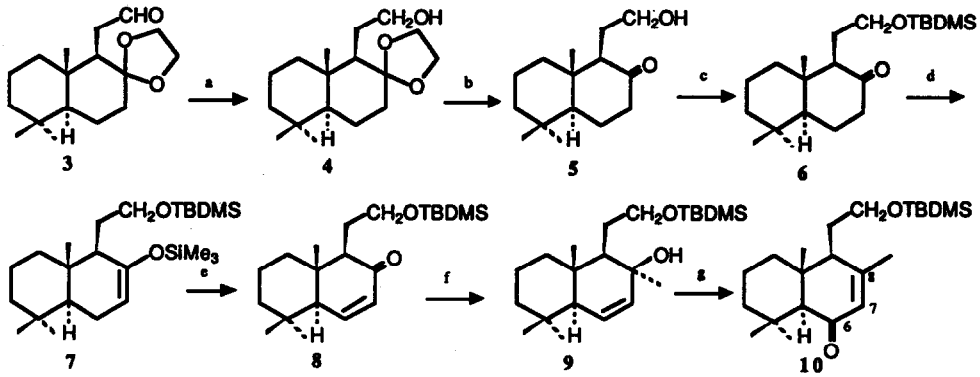


1

To minimize neighbouring-group side reactions such as those previously encountered, we chose to investigate functionalization of the octalones **8** or **10**, both accessible (Scheme 1) from the previously described dioxolane aldehyde **3**.[1]

Reduction of aldehyde **3** with $NaBH_4$, followed by dioxolane cleavage gave carbinol **5**, mp 76-77°C, which was protected as the *t*-butyldimethylsilyl ether **6**. Introduction of the 6,7-alkene by $Pd(OAc)_2$ oxidation of enol silane **7**,[5] followed by stereospecific MeLi addition, gave carbinol **9**. Oxidative transposition with PCC[6] produced enone **10**, mp 60°C, in 92% yield.[7]

Scheme 1



a) $NaBH_4$, 2 eq, EtOH, rt, 98%; b) 1N HCl, THF/H_2O, rt, 82%; c) TBDMSCl, 1.2 eq., imidazole 2 eq, THF, rt, overnight, 95%; d) LDA, 5 eq, THF, -78°C, 1h, then $ClSiMe_3$, 2 eq, -78°C to 0°C, 72%; e) $Pd(OAc)_2$, 1.2eq, MeCN, rt, overnight, 85%; f) MeLi, 2 eq,.ether, 0°C, 1 h, 98%; g) PCC, 4.5eq., NaOAc, CH_2Cl_2, 0°C,15 min, then, rt, 2 h, 91%.

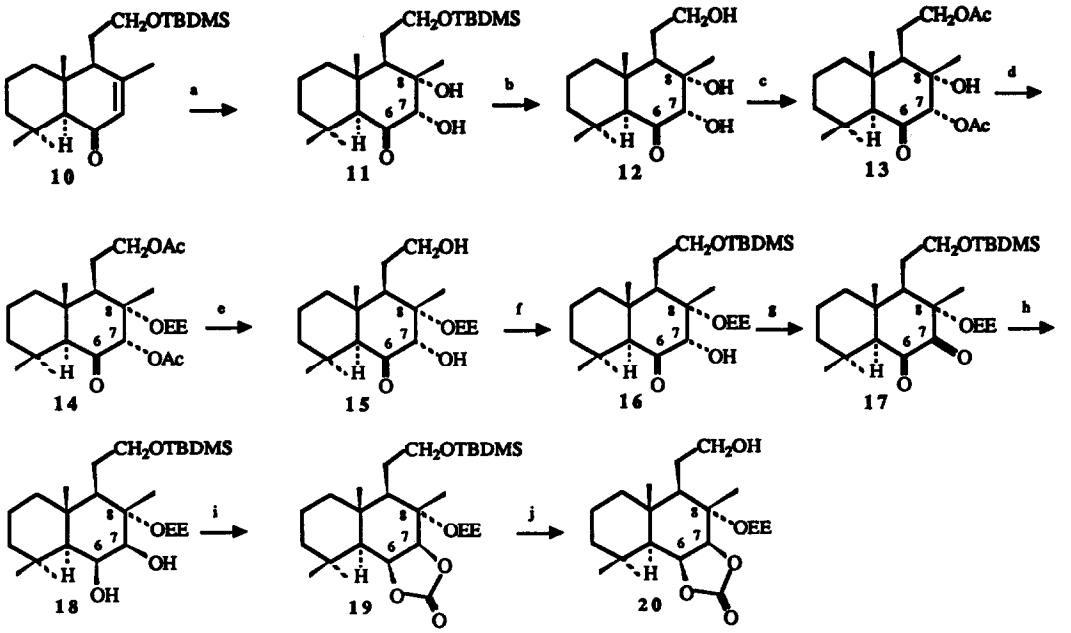
Our strategy was to fully elaborate the 6β,7β,8α-triol functionality in the B-ring of **10** prior to the construction of the diene side chain, as in Scheme 2.

To this end, catalytic OsO_4-NMO[8] oxidation of **10** gave the diol **11**, mp 95°C. To ascertain the stereochemistry of the *cis* diol **11**, 2D nuclear Overhauser experiments were carried out with triol **12**, mp 144-145°C, in which the methyl signals of the proton NMR were well separated. NOE effects were observed between the C(20)-Me and the C(17)-Me, and also between the C(20)-Me and the C(19)-Me, showing that the *cis*-hydroxylation reaction had occurred, as anticipated, on the less hindered α-side of the molecule.

Acetylation of triol **12** with Ac_2O-py gave diacetate **13**, mp 134-135°C, from which the tertiary alcohol was protected as ethoxyethyl ethers **14** present as the mixture of ethoxyethyl epimers. Cleavage of the acetates with 2% KCN in MeOH[8] gave ketol **15**. Selective silylation of the primary hydroxyl now produced **16** which on Dess-Martin oxidation[10] gave dione **17**. Reduction of this dione **17** with excess $NaBH_4$ in EtOH provided the 6β,7β-diol **18** which was then reacted with one equivalent of $COCl_2$ in PhMe in the presence of pyridine to give the cyclic carbonate **19**.[11] Desilylation of the primary alcohol with *n*-Bu_4NF gave the key intermediate **20**.

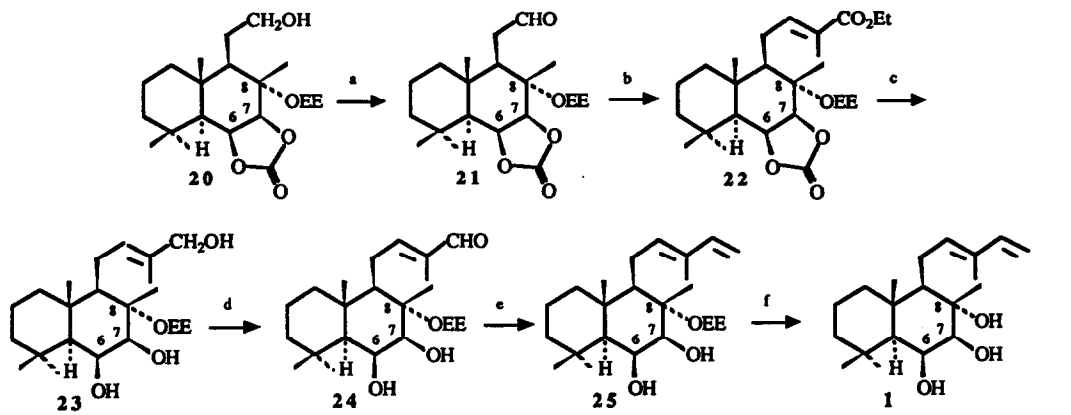
Our synthesis was completed by side chain elaboration from the aldehyde **21**, prepared in high yield by Dess-Martin oxidation[10] of carbinol **20** (Scheme 3). A Horner-Emmons condensation of **21** with the sodio derivative of ethyl 2-diethylphosphonopropionate in PhMe gave the *E*-olefin **22** as major product (*E*/*Z*>95/5). Reduction of the ester function with $LiAlH_4$ was accompanied by carbonate cleavage to provide triol **23**.

Scheme 2



a) OsO_4, catalytic, NMO, 3 eq., t-BuOH, acetone, H_2O, rt, 48 h, 55%; b) TBAF, 1 eq., THF, rt, 3 h, 90%; c) Ac_2O, excess, py, rt, overnight, 86%; d) ethylvinyl ether, 5 eq., CSA, catalytic, CH_2Cl_2, overnight, 70%; e) 2 % KCN, MeOH, overnight, 91%; f) TBDMSCl, 1.2 eq., imidazole, 3 eq., THF, rt, overnight, 96%; g) Dess-Martin periodinane, 1 eq., CH_2Cl_2, rt, 1 h, 90%; h) $NaBH_4$, 5 eq., EtOH, rt, overnight, 64%; i) $COCl_2$, 1.2 eq., toluene, py, rt, overnight, 92%; j) TBAF, 1 eq., THF, rt, 3 h.91%.

Scheme 3



a) Dess-Martin periodinane, 1 eq., CH_2Cl_2, rt, 1 h, 90%; b) ethyl 2-diethylphosphonopropionate, 3 eq., NaH, 3 eq., toluene, 80°C, 1 h, 56%; c) $LiAlH_4$, 2 eq., ether, rt, 3 h, 70%; d) Dess-Martin periodinane, 1 eq., CH_2Cl_2, rt, 1 h, 92%; e) $H_2C{=}PPh_3$, 5 eq., THF, 0°C, 3 h, 51%; f) PPTs, catalytic, MeOH, rt, 30 min., 98%.

The allylic primary alcohol was selectively oxidised with one equivalent of Dess-Martin periodinane to give aldehyde **24**. Wittig reaction with excess methylenetriphenylphosphorane converted **24** to **25**. Mild hydrolysis of the ethoxyethyl protecting group with PPTS in MeOH, provided pure racemic triol diene **1**.

The spectroscopic data (^{1}H-NMR, ^{13}C-NMR, UV, MS)[12] obtained for synthetic (±)-**1** were identical to those described for crotomachlin[2] and 6β,7β-dihydroxy-12E-abienol.[3] The present work thus unambiguously establishes the 6β,7β,8α-triol stereochemistry in this natural product.

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References and Notes

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4 Professor S. Isoe (Osaka City University) has recently communicated to us that his group has synthesized 8)epicrotomachlin having a C(8)β-hydroxyl, thereby independently concluding that crotomachlin has the C(8)α-configuration.
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7 Enone **10**: $C_{22}H_{40}O_2Si$, Calc. %: C 72.47, H 11.06, found C 72.27, H 10.83; MS, CI: MH^+ 365, m/z 361, 313, 257; IR cm^{-1}: 1682 ($\nu_{C=O}$), 1635 (C=C), 1100 (C-O); UV $\lambda_{max\ EtOH}$: 238 nm, ε 11 617; ^{1}H NMR, 250 MHz, δ ppm: 0.06 (6H, *s*, 2 $SiCH_3$), 0.83 (3H, *s*, C-20H_3), 0.90 (9H, *s*, tBu), 1.11 (3H, *s*, C-19H_3), 1.16 (3H, *s*, C-18H_3), 1.90 (3H, *s*, C-17H_3), 1.0-2.2 (9 H, *m*, CH, CH_2), 2.05 (1H, *s*, C-5H), 3.66 and 3.73 (2H, 2*m*, CH_2-12), 5.73 (1H, *q*, J=1, H-7); ^{13}C NMR, δ ppm: -5.18 (2$SiCH_3$), 14.48 (CH_3), 18.02 (CH_2), 21.41 (CH_3), 21.93 (CH_3), 26.09 (CH_2), 27.16 (tBu), 32.18 (C), 33.32 (CH_3), 38.61 (C), 38.80 (CH_2), 42.72 (C), 43.05 (CH_2), 52.36 (CH), 63.38 (CH), 64.84 (C-12H_2), 128.83 (C-7H), 157.16 (C-6), 199.44 (C=O).
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11 Carbonate **20**: $C_{21}H_{36}O_5$; MS CI: MH^+ 385, peaks at 367, 339, 295, 277, 251, 233; IR cm^{-1}: 3250 (OH), 1780 ($\nu_{C=O}$), 1015, 1035, 1080 (C-O); ^{1}H NMR, 250 MHz, one of the 1'-epimer, δ ppm: 1.05 (3H, *s*, C-20H_3), 1.10 (3H, *s*, C-19H_3), 1.14 (3H, *s*, C-18H_3), 1.19 (3H, *t* , J=7, $CH_2\underline{CH_3}$), 1.33 (3H, *d*, J=5, $CH\underline{CH_3}$), 1.43 (3H, *s*, C-17H_3), 0.9-1.90 (10 H, *m*, CH, CH_2), 3.47 (2H, *m*, $\underline{CH_2}CH_3$), 3.47 and 3.75 (2H, 2*m*, CH_2-12), 4.58 (1H, *d*, J=7, H-7), 5.05 (1H, *dd*, J=4, J'=7, C-6H), 5.17 (1H, *q*, J=5, C-1'H).
12 Synthetic **1**: $C_{20}H_{34}O_3$, HR CIMS (CH_4+NH_3) MNH_4^+ calc.341.2929 found 341.2890, MH+ calc. 323.2586 found 323.2572, UV $\lambda_{max\ EtOH}$: 231.8 nm (ε 18.000); ^{1}H NMR, 250 MHz, δ ppm: 1.0 (3H, *s*, C-18H_3), 1.22 (6H, *s*, C-4αH_3, C-4βH_3), 1.37 (3H, *s* , C-17H_3), 1.81 (3H, *s*, C-16H_3), 0.8-1.8 (8H, *m*,, CH_2), 2.29 and 2.49 (2H, ABXY, C-11H_2), 3.43 (1H, *d*, J=4, C-7H), 4.43 (1H, *broad t*, C-6H), 4.93 (1H, *d*, J=9, C-15H), 5.08 ((1H, *d*, J=18, C-15H), 5.60 (1H, *broad t*, J=6, C-12H),6.35 (1H, dd, J=18, J'=9, C-14H); ^{13}C NMR, δ ppm: 11.96 (CH_3), 16.80 (CH_3), 18.77 (CH_2), 19.52 (CH_3), 23.41 (CH_2), 24.02 (CH_3), 33.45 (CH_3), 34.08 (C), 39.76 (C), 42.25 (CH_2), 43.74 (CH_2), 55.77 (CH), 60.58 (CH), 70.93 (CH), 77.28 (C), 80.67 (CH), 110.73 (C-15H_2), 133.0 (C-13), 135.60 (C-12H), 141.54 (C-14H).

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