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Stereoselective synthesis of the C_1–C_{13} segment of dolabelide B

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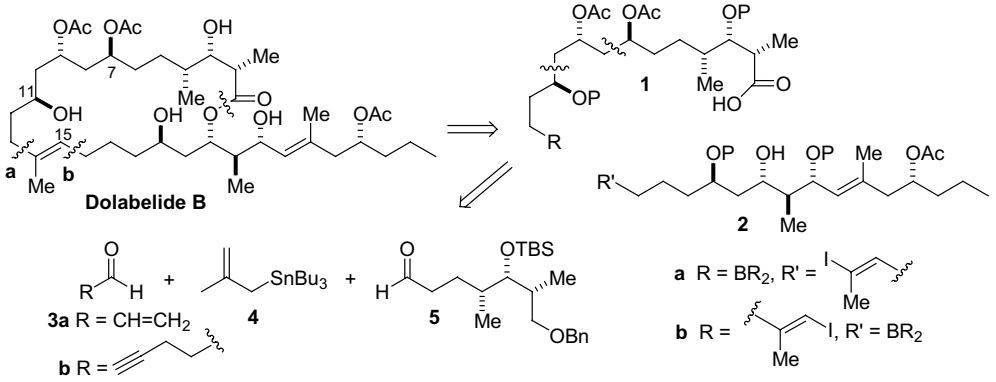
Abstract—The efficient construction of the C_1–C_{13} segment of dolabelide B is described. A key element of the synthesis entails BITIP catalyzed asymmetric methallylation to establish the C_7 stereocenter, which was then used to direct the stereoselective installation of the C_9 and C_{11} centers through Evans reduction and 1,5-*anti* aldol condensation, respectively.

The marine natural product dolabelide B is a member of a small family of macrolides isolated from the sea hare *Dolabella auricularia*, which has been shown to exhibit cytotoxicity against $HeLaS_3$ cell lines with an IC_{50} value of 1.3 μg/mL.[1] The biological activity of dolabelide B and its limited availability from natural sources have prompted a number of recent synthetic studies directed toward this structure.[2–4] Herein, we report a concise stereoselective synthesis of the C_1–C_{13} segment of dolabelide B.

We envisioned the dolabelides as potentially being derived from the union of two subunits, **1** and **2** (Scheme 1), arising from bond disconnection at the macrolactone and about the C_{14}–C_{15} olefin. Disconnection about the C_{14}–C_{15} double bond to give Suzuki coupling precursors[5] can be viewed taking place on either side of the olefin, and both approaches were investigated during the course of our study. However, as the synthesis progressed, continued evaluation of our approach lead us to ultimately choose disconnection across the C_{13}–C_{14} bond (disconnection **a**) as the most prudent course.

Our past experience in synthesizing skipped triol structures like that found in subunit **1** suggested that the desired stereochemical relationship could be constructed from aldehydes **3** and **5** through a sequence of asymmetric allylation using a 2-substitued allylstannane reagent,



Scheme 1. Retrosynthetic analysis of dolabelide B.

Keywords: Dolabelide; Asymmetric synthesis; Allylation; Hydroformylation.
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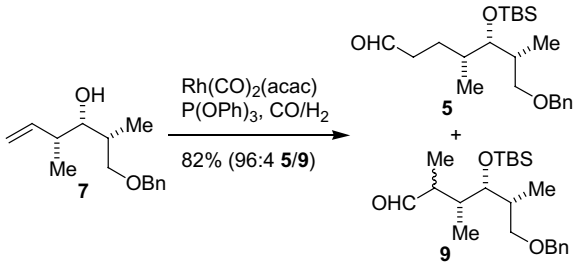
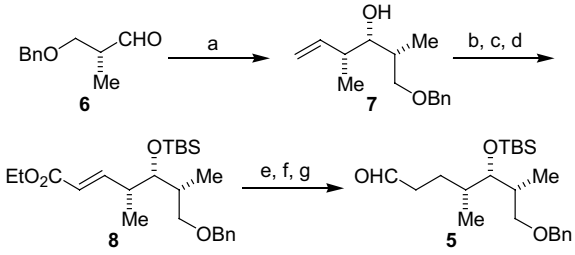
aldol reaction with 1,5-induction, and 1,3-reduction.[6] A process by which the initial hydroxyl group is introduced with a high degree of stereoselection is vital, given that this stereocenter will be used to control the stereochemistry of the remaining stereocenters of the triol segment. We have found the catalytic asymmetric allylation (CAA) reaction using the catalyst prepared from BINOL and titanium isopropoxide (BITIP) to be ideally suited for establishing remote secondary hydroxyl groups in a highly stereoselective fashion.[7–9] We were hopeful, therefore, that the CAA reaction would fulfill this requirement in the present instance.

Our approach commenced with the synthesis of aldehyde **5** as shown in Scheme 2. The stereochemical relationship of the triad found in this segment lends itself well to synthesis via crotylstannylation chemistry previously developed in our laboratories.[10] Thus, treatment of aldehyde **6** with $TiCl_4$ and (*Z*)-crotyl tributyltin provided **7** in good yield and diastereoselectivity. After protection of the hydroxyl group, the backbone was extended by one carbon through a series of transformations involving oxidative cleavage of the terminal olefin followed by two-carbon homologation and net reduction[11] to arrive at aldehyde **5**. Although this sequence was successful at producing the desired aldehyde in an overall yield of 30% from **6**, the overall process was far more cumbersome and lengthy than we desired. Indeed, we recognized that overall this six step sequence was equivalent to a reductive carbonylation of olefin **7**. Therefore, a more direct approach involving hydroformylation was investigated in order to streamline the production of intermediate **5**. Hydroformylation of terminal olefins is a powerful reaction type; however, it most commonly results in mixtures of linear and branched regioisomers. A thorough search of the literature suggested that, in this instance, hydroformylation of olefin **7** might be expected to proceed with some degree of regioselectivity to favor the linear product due to the steric environment defined by the methyl substituent at C_4.[12] Indeed, in the event, the reaction proved exceptionally regioselective giving a linear/branched ratio of 96:4 in favor of the desired product, which was isolated by chromatography in 82% yield (Scheme 3). This three-step sequence (crotyl addition, silyation, and hydroformylation) was easily scaled to furnish multigram quantities of aldehyde **5** from compound **6** in an overall yield of 54% and as a single isomer.

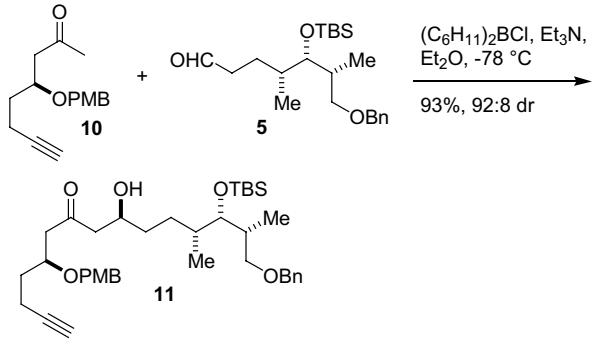


Scheme 3. Hydroformylation of **7**.

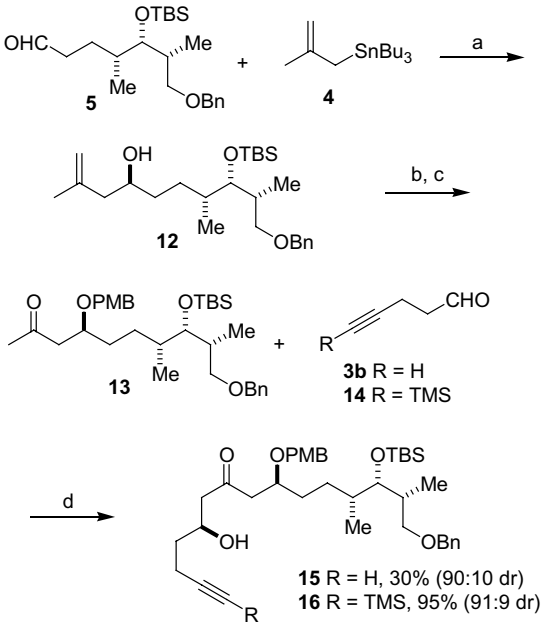
The synthesis of the triol portion of subunit **1** can be approached from either of the two directions in which the stereochemistry of the hydroxyl bearing carbon at either the C_7 or C_{11} stereocenters is set through asymmetric methallylation. While an approach that first establishes the C_{11} hydroxyl group would be considered more convergent, experimentation revealed that the subsequent aldol reaction between methyl ketone **10** and aldehyde **5** required a three-fold excess of **5** to achieve acceptable conversion (Scheme 4). Therefore, a more linear approach was taken to minimize consumption of such an advanced intermediate, as shown in Scheme 5. BITIP catalyzed methallylation of **5** gave alcohol **12** in 96% yield and with 94:6 diastereoselectivity. After protection of the resulting hydroxyl group as the PMB ether, the methylene group was oxidatively cleaved to give the aldol precursor **13**. Aldol condensation of ketone **13** with aldehyde **3b** using conditions developed by Paterson et al.[13] afforded the desired 1,5 *anti* product with a pleasing 90:10 diastereomeric ratio, but in a disappointing 30% yield. The meager yield was attributed to decomposition of aldehyde **3b** during the reaction, and a significant improvement was achieved by using the more robust aldehyde **14**. Likewise, condensation with acrolein was successful and afforded the desired 1,5-diol in 83% yield and as a single isomer (Scheme 6). The resulting alcohol **17** was protected as the silyl ether and the PMB group was removed with DDQ to unmask the directing group for *anti* reduction. Reduction of the β-hydroxy ketone with SmI_2/methanol[14] occurred essentially quantitatively, however the diastereomeric ratio was only 2:1 in favor of the desired *anti* product. We



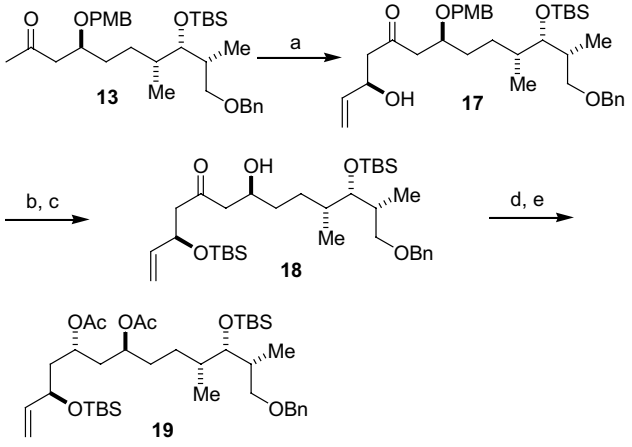
Scheme 2. Reagents and conditions: (a) (*Z*)-crotyltributyltin, $TiCl_4$, −90 °C, 2.5 h, 80% (15:1 dr); (b) TBSOTf, Et_3N, CH_2Cl_2, −30 to 0 °C, 1 h, 83%; (c) O_3, CH_2Cl_2, −78 °C, 15 min; PPh_3, rt, 2 h; (d) $(C_6H_5)_3P=CHCO_2C_2H_5$, CH_2Cl_2, rt, 18 h; (e) SmI_2, MeOH, DMA, 0 °C, 15 min, 55% (three steps); (f) DIBAL, THF, −78 °C, 4 h; (g) $(COCl)_2$, DMSO, Et_3N, −78 °C, 4 h, 83% (two steps).



Scheme 4. C_7–C_8 bond construction via 1,5-*anti* aldol condensation.



Scheme 5. Reagents and conditions: (a) (*R*)-(+)-1,1′-bi-2-naphthol, $Ti(OiPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 5 days, 96% (94:6 dr); (b) NaH, *p*-methoxybenzyl bromide, KI, THF, 0 °C, 6 h, 91%; (c) OsO_4, NMO, *t*-BuOH/THF/H_2O, rt, 1.5 h; $NaIO_4$, rt, 2 h, 89%; (d) $(C_6H_{11})_2BCl$, Et_3N, Et_2O, −78 to −20 °C, 22 h.



Scheme 6. Reagents and conditions: (a) acrolein, $(C_6H_{11})_2BCl$, Et_3N, Et_2O, −78 to −20 °C, 22 h, 83% (single isomer); (b) TBSOTF, 2,6-lutidine, THF, 0 °C, 1 h, 96%; (c) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 0 °C, 40 min, 89%; (d) $Me_4NBH(OAc)_3$, 1:1 acetonitrile/AcOH, −15 °C, 5 h, 85%; (e) Ac_2O, DMAP, pyridine, rt, 18 h, 94%.

have found,[15–17] as have others,[18,19] that the *syn*/*anti* ratio obtained from β-directed reduction of ketones with SmI_2 can be greatly influenced by a number of factors, including the nature of the neighboring functionality, solvent, additives, and proton source. In many cases, the diastereoselectivity can be increased, or even switched, by attenuating one or more of these factors. Unfortunately, all attempts to improve the *syn*/*anti* selectivity of this particular SmI_2 mediated reduction failed. Improved selectivity was ultimately achieved using tetramethylammonium triacetoxyborohydride[20] to give the diol as a 26:1 (*anti*/*syn*) mixture that was separable by chromatography, thereby affording the desired isomer in 85% yield. Completion of the synthesis of this segment was accomplished uneventfully by acetylation of the resulting diol, providing **19** with all stereocenters in place, in a total of 11 linear steps with an overall yield of 24% from compound **5**.[21,22] Future events leading to subunit coupling will require the removal of the benzyl protecting group found at C_1, and oxidation of the alcohol to the acid. Hydroboration of the olefin at C_{12}–C_{13} with 9-BBN is expected to provide the appropriate Suzuki coupling partner for ring closure.

Acknowledgements

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22. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass data. Spectroscopic and physical characterization data of selected compounds: Compound **5**: $R_f = 0.40$ (15% EtOAc/hexanes); $[\alpha]_D^{20}$ +10.2 (*c* 0.95, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.74 (t, $J = 1.8$ Hz, 1H), 7.35–7.26 (m, 5H), 4.49 (ABq, $J_{AB} = 11.9$ Hz, $\Delta v = 14.4$ Hz, 2H), 3.59–3.46 (m, 2H), 3.30 (dd, $J = 8.9$, 7.4 Hz, 1H), 2.55–2.30 (m, 2H), 2.04–1.89 (m, 1H), 1.78–1.42 (m, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.04 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.6, 138.7, 128.3, 127.5, 127.4, 76.9, 73.0, 72.9, 42.3, 37.9, 35.9, 26.8, 26.1, 18.4, 15.0, 14.1, −3.8, −4.1; IR (neat) 2931, 1726, 1458, 1254, 1097, 1057, 774, 698 cm^{-1}. Anal. Calcd for $C_{22}H_{38}O_3Si$ requires C, 69.79; H, 10.12. Found: C, 69.52; H, 10.27. Compound **7**: $R_f = 0.60$ (35% EtOAc/hexanes); $[\alpha]_D^{20}$ −0.8 (*c* 1.09, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (m, 5H), 5.91–5.79 (m, 1H), 5.06–5.03 (m, 1H), 5.00 (dd, $J = 1.1$, 1.1 Hz, 1H), 4.51, (s, 2H), 3.66 (dd, $J = 9.1$, 4.3 Hz, 1H), 3.49 (dd, $J = 9.1$, 6.2 Hz, 1H), 3.40 (ddd, $J = 6.9$, 4.8, 4.8 Hz, 1H), 3.23–3.21 (m, 1H), 2.37–2.27 (m, 1H), 2.00–1.85 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.96 (d, $J = 7.0$, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 142.2, 137.7, 128.4, 127.7, 127.6, 114.0, 78.8, 74.7, 73.5, 40.9, 35.6, 14.4, 13.2; IR (neat) 3487 (broad), 2965, 1455, 1092, 737, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46. Found: C, 76.66; H, 9.56. Compound **12**: $R_f = 0.26$ (5% EtOAc/hexanes); $[\alpha]_D^{20}$ +8.0 (*c* 1.28, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5H), 4.90–4.80 (m, 2H), 4.40 (ABq, $J_{AB} = 11.9$ Hz, $\Delta v = 9.9$ Hz, 2H), 3.72–3.62 (m, 1H), 3.56 (dd, $J = 8.9$, 4.5 Hz, 1H), 3.51 (dd, $J = 5.9$, 2.1 Hz, 1H), 3.29 (dd, $J = 8.2$, 8.2 Hz, 1H), 2.24–1.91 (m, 3H), 1.76 (s, 3H), 1.72 (br s, 1H), 1.62–1.37 (m, 4H), 1.24–1.10 (m, 1H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.89–0.87 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 142.8, 138.8, 128.3, 127.5, 127.4, 113.5, 77.5, 73.1, 72.9, 68.9, 46.1, 37.9, 36.5, 35.4, 30.7, 26.1, 22.4, 18.4, 15.2, 14.3, −3.7, −4.1; IR (neat) 3456 (broad), 2931, 1456, 1254, 1097, 836, 773 cm^{-1}. Anal. Calcd for $C_{26}H_{46}O_3Si$ requires C, 71.83; H, 10.67. Found: C, 72.10; H, 10.65. Compound **17**: $R_f = 0.38$ (25% EtOAc/hexanes); $[\alpha]_D^{20}$ +22.5 (*c* 1.63, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 7H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.82 (ddd, $J = 16.0$, 10.5, 5.5 Hz, 1H), 5.25 (app dt, $J = 17.2$, 1.4 Hz, 1H), 5.12 (app dt, $J = 10.5$, 1.4 Hz, 1H), 4.57–4.35 (m, 5H), 3.90–3.84 (m, 1H), 3.78 (s, 3H), 3.53 (dd, $J = 9.16$, 4.7 Hz, 1H), 3.48 (dd, $J = 6.1$, 2.7 Hz, 1H), 3.28, (dd, $J = 8.7$, 7.6 Hz, 1H), 3.10 (br d, $J = 3.8$ Hz, 1H), 2.76–2.42 (m, 4H), 1.99–1.88 (m, 1H), 1.60–1.35 (m, 4H), 1.25–1.08 (m, 1H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.02 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 210.2, 159.2, 138.9, 138.7, 130.3, 129.4, 128.3, 127.5, 127.4, 114.9, 113.7, 77.2, 75.5, 73.0, 72.9, 71.3, 68.5, 55.2, 50.1, 48.4, 37.8, 36.6, 32.4, 29.9, 26.1, 18.4, 15.3, 14.3, −3.7, −4.1; IR (neat) 3453 (broad), 2931, 1710, 1514, 1250, 1093, 1038, 836, 757 cm^{-1}. Anal. Calcd for $C_{36}H_{56}O_6Si$ requires C, 70.55; H, 9.21. Found: C, 70.36; H, 9.28. Compound **19**: $R_f = 0.64$ (25% EtOAc/hexanes); $[\alpha]_D^{20}$ +7.9 (*c* 0.1.54, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.34–7.25 (m, 5H), 5.82 (ddd, $J = 16.9$, 10.4, 6.1 Hz, 1H), 5.17 (app. dt, $J = 17.1$, 1.4 Hz, 1H), 5.08–4.99 (m, 2H), 4.94–4.86 (m, 1H), 4.48 (ABq, $J_{AB} = 12.1$ Hz, $\Delta v = 9.1$ Hz, 2H), 4.13 (ddd, $J = 6.1$, 6.1, 6.1 Hz, 1H), 3.52 (dd, $J = 9.0$, 4.6 Hz, 1H), 3.47 (dd, $J = 6.4$, 2.6 Hz, 1H), 3.28 (dd, $J = 9.0$, 7.6 Hz, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.95–1.32 (m, 9H), 1.20–1.08 (m, 1H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.83 (d, $J = 6.7$ Hz, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.6, 170.3, 140.5, 138.7, 128.3, 127.4, 114.4, 77.1, 73.1, 73.0, 70.7, 70.1, 67.3, 43.2, 38.8, 37.9, 36.3, 33.0, 30.1, 26.1, 25.8, 21.1, 18.4, 18.2, 15.2, 14.0, −3.7, −4.1, −4.4, −4.9; IR (neat) 2931, 1741, 1470, 1363, 1249, 1095, 1027, 837, 775 cm^{-1}. Anal. Calcd for $C_{38}H_{68}O_7Si_2$ requires C, 65.85; H, 9.89. Found: C, 65.80; H, 9.92.