Formal Total Synthesis of (+)-Methynolide

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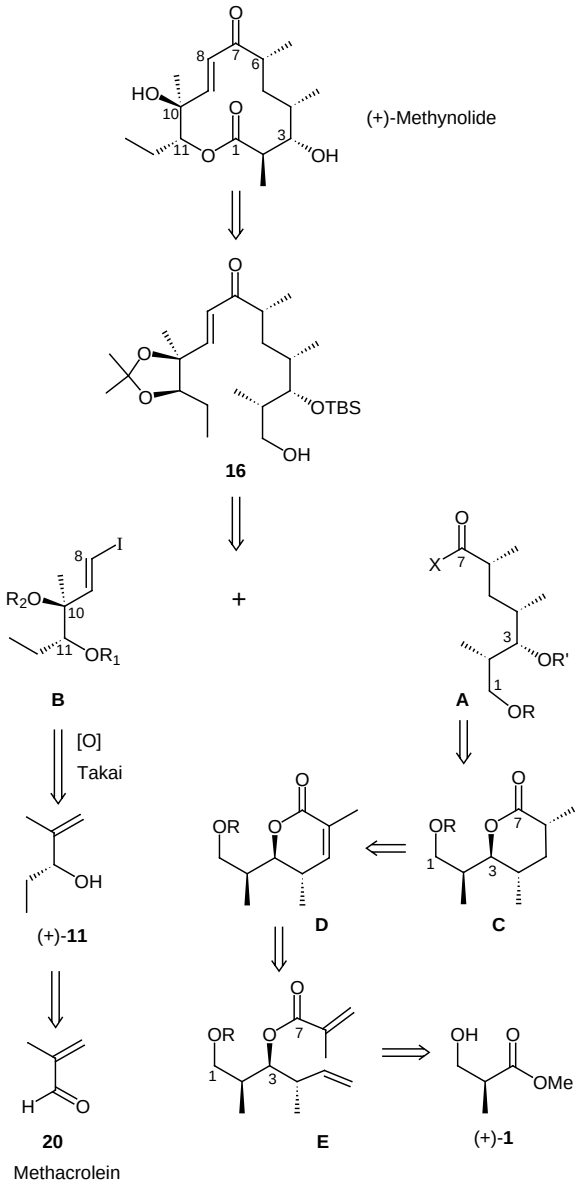
Abstract: A convergent total synthesis of (+)-methynolide was achieved in 23 steps highlighted by a ring-closing metathesis, a Takai reaction, a Sharpless kinetic resolution of an allylic alcohol and a crotylboration.

Key words: macrocycles, crotylboronate, metathesis, Takai reaction, kinetic resolution

Complex molecules like macrolide antibiotics with multiple stereocenters have received much attention due to their powerful biological activities.[1] One member of this macrolide family is methynolide, the aglycone of methymycin.[2] The first total synthesis of methymycin (31 steps, overall yield of 0.12%) by Masamune[3] as well as subsequent syntheses of methynolide or its corresponding seco-acid by the groups of Grieco,[4] Yamaguchi,[5] White,[6] Yonemitsu[7] and Ditrich[8] combined two enantioenriched fragments giving an open-chain precursor which was cyclized by an intramolecular esterification[3–5,8] or an intramolecular Wittig-type reaction.[7] Three of these syntheses combined the chiral C_1–C_8 fragment with the C_9–C_{11} fragment[3,7,8] and three of them combined the C_1–C_7 fragment with the C_8–C_{11} fragment.[4-6] Linear strategies were also reported by Ireland,[9] Vedejs[10] and Bartlett.[11]

For our part, we planned the synthesis of (+)-methynolide from the previously synthesized intermediate **16**.[4,6] The retrosynthetic analysis of this intermediate suggested a convergent approach, i. e., the assemblage of **16** from two enantioenriched fragments **A** (C_1–C_7) and **B** (C_8–C_{11}). These two fragments would be linked by addition of a vinyl lithium reagent, derived from the vinyl iodide **B**, to the carboxylic functionality of **A**. The synthesis of the C_1–C_7 fragment was envisaged from lactone **C** that would be obtained from the unsaturated lactone **D** that could be produced from the corresponding diene **E** by a ring-closing metathesis (RCM). The precursor of this diene is the commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (+)-**1**. The synthesis of fragment **B** was envisaged by a Takai[12] reaction applied to an aldehyde that can be obtained by dihydroxylation and subsequent selective oxidation of the enantioenriched allylic alcohol (+)-**11**. Alcohol (+)-**11** will be synthesized from methacrolein **20** (Scheme 1).



Scheme 1 Retrosynthetic scheme

The synthesis of the C_1–C_7 fragment **A** was achieved starting from methyl (*2S*)-3-hydroxy-2-methylpropionate (+)-**1** (Scheme 2). The β-hydroxy ester (+)-**1** was transformed to the silyl ether (+)-**2** in quantitative yield by using *tert*-butyldimethylsilyl chloride (TBSCl, imidazole, DMF) that was then converted to aldehyde (+)-**3**[13] in two steps by reduction with DIBAL-H followed by pyr·SO_3 oxidation. The overall yield for the conversion of (+)-**1** to aldehyde (+)-**3** was 82%. Control of the stereogenic cen-

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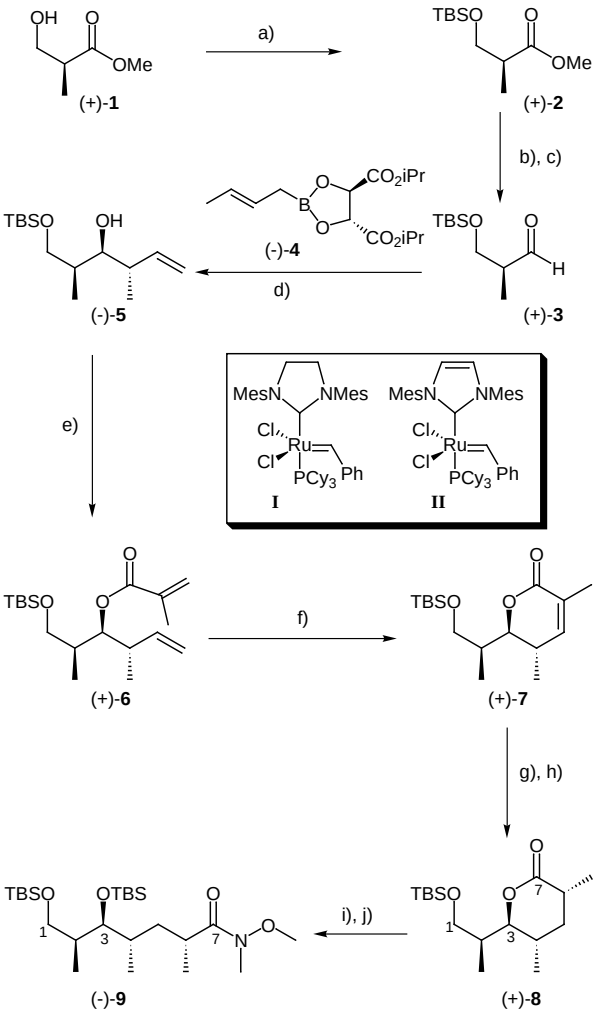
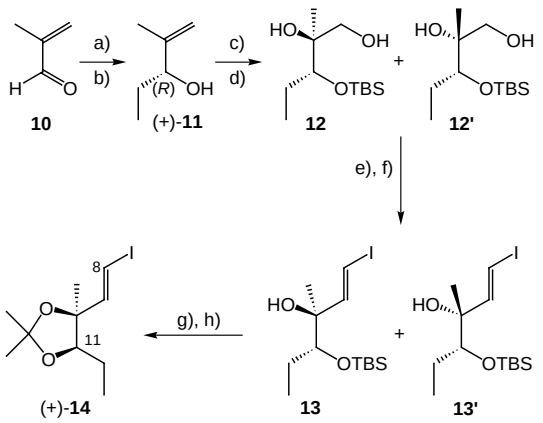
ters at C_3 and C_4 was achieved by addition of crotylboronate (–)-**4**[14] to aldehyde (+)-**3**. Compound (–)-**5**[14] was isolated in 81% yield and with a diastereomeric excess up to 95%.[15] The next step was the transformation of (–)-**5** to the precursor of the unsaturated lactone (+)-**7**. When (–)-**5** was treated with methacryloyl chloride at 0 °C in the presence of triethylamine and a catalytic amount of DMAP, the unsaturated diene ester (+)-**6** was isolated in 79% yield. To transform the unsaturated diene ester (+)-**6** to the corresponding unsaturated lactone, several RCM catalysts were examined. The use of catalyst **I**[16] (15 mol%, CH_2Cl_2, reflux, 14 h) led to lactone (+)-**7** in 77% yield for a conversion of 80%. A better result was obtained with catalyst **II**[17] (15 mol%, CH_2Cl_2, reflux, 14 h) as lactone (+)-**7** was isolated in 98% yield for complete conversion of (+)-**6**. After hydrogenation (H_2, PtO_2) and treatment with LDA, a 2.3:1 mixture of lactones (+)-**8** and (+)-**8′** (epimer at C_6) was obtained in 97% yield. These two compounds were separated by flash chromatography,[18] and lactone (+)-**8** was transformed to the required amide (–)-**9** in two steps. After treatment of lactone (+)-**8** with Weinreb's amine hydrochloride in the presence of trimethylaluminium,[19] the resulting hydroxy amide was protected by using *tert*-butyldimethylsilyl chloride in the presence of $AgNO_3$[20] to produce the desired amide (–)-**9** in 70% yield for the two steps. By using these two key steps reactions, a crotylboration and a ring-closing metathesis, methyl (*2S*)-3-hydroxy-2-methylpropionate (+)-**1** was transformed to the desired amide (–)-**9** in 10 steps with an overall yield of 23%.

The C_8–C_{11} fragment **B** was synthesized from methacrolein **10** (Scheme 3). When methacrolein **10** was treated with ethylmagnesium bromide in ether, the resulting alcohol **11**, isolated in 68% yield, was converted to (+)-**11** of 90% enantiomeric excess,[21] by using a Sharpless kinetic resolution[22] [Ti(*i*PrO)$_4$, (+)-DIPT, *t*-BuOOH, MS 4 Å]. After protection of the alcohol functionality (*tert*-butyldimethylsilyl chloride) the silyl ether was treated with OsO_4 in the presence of NMO (acetone, H_2O) to produce the monoprotected triols **12** and **12′** in 75% yield as 5.5:1 mixture of two diastereomers which were not separable.[23] After oxidation of the mixture of **12** and **12′** (pyr·SO_3, DMSO, Et_3N), the resulting aldehydes were transformed to vinyl iodides **13** and **13′** in 78% yield by using a Takai reaction[12] (HCI_3, $CrCl_2$). The stereoselectivity $E/Z > 97:3$ was determined by ^{1}H NMR analysis. Compounds **13** and **13′** were then deprotected (TBAF) and the resulting diols were transformed to the ketal derivatives by using 2,2-dimethoxypropane (PPTS, acetone). The two diastereomeric products were separated by flash chromatography on silica gel and ketal (+)-**14**[24] was isolated in 74% yield.

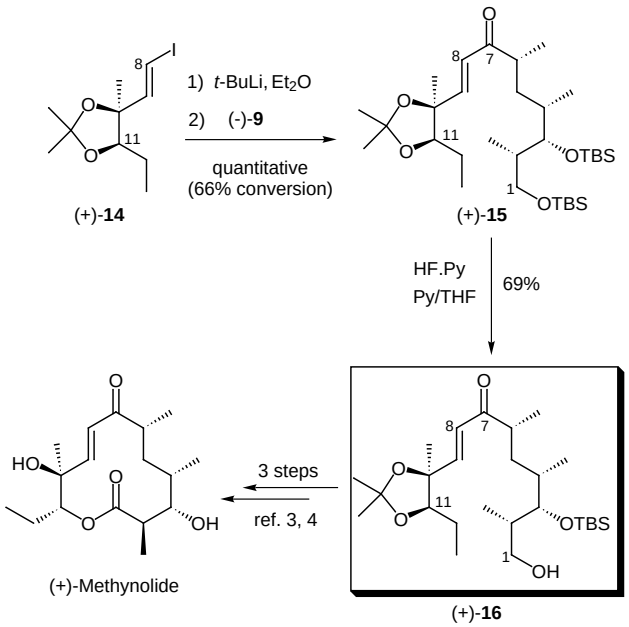
The transformation of methacrolein **10** to (+)-**14** was achieved in 8 steps with an overall yield of 27%. With both building blocks (–)-**9** and (+)-**14** in hand, we next completed the carbon skeleton of methynolide by addition of vinyllithium reagent **14′**, which was obtained from the corresponding vinyl iodide by metal-halogen exchange (*t*-BuLi, ether, –78 °C), to the previously obtained amide (–)-**9**. The coupling product (+)-**15** was obtained in quantitative yield.[25] A selective deprotection to the known intermediate (+)-**16**[26] was achieved (Scheme 4) by treatment of (+)-**15** with HF·pyridine in a mixture of pyridine–THF. As (+)-**16** has been previously converted to methynolide in 3 steps,[3,4] a formal total synthesis of methynolide is thus achieved in 23 steps.



Scheme 2 a) TBSCl, imidazole, DMF. b) DIBAL-H, THF. c) pyr·SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 82% (3 steps). d) (–)-**4**, MS 4Å, toluene, 81%. e) methacryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 79%. f) **I** or **II** (15 mol%), CH_2Cl_2, reflux, 96–98%. g) H_2 (4 atm), PtO_2, EtOH, **8**/**8′** = 1/1. h) LDA, –78 °C, 1.5 h; then 10% aqueous citric acid, –78 °C, **8** (65% yield, 2 steps) and **8′** (32% yield, 2 steps). i) Me(MeO)NH.HCl, $AlMe_3$, CH_2Cl_2. j) TBSCl, $AgNO_3$, DMF, 70% (2 steps).



Scheme 3 a) EtMgBr, Et_2O, 68%. b) $Ti(OiPr_4)$, (+)-DIPT, *t*-BuOOH, MS 4 A, CH_2Cl_2, -20 °C, 91% (90% ee). c) TBSCl, imidazole, DMF, 81%. d) OsO_4, NMO, acetone, H_2O, 92%. e) pyr·SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, quantitative yield. f) $CrCl_2$, CHI_3, THF, 78%. g) TBAF, THF, 87%. h) 2,2-dimethoxypropane, PPTS, acetone, quantitative yield; separation of the two diastereomers.



Scheme 4

Compared to other syntheses of methynolide, the synthesis reported in this paper represents one of the shortest routes to the 11-membered macrocyclic lactone.

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(24) The ketalization was quantitative and the separation of (+)-**14** and its C_{10} epimer was performed by flash chromatography on silica gel (hexanes–Et_2O, 100:0 to 90:10).

(25) For a conversion of 66% of (−)-**9**.

(26) Analytical data of (+)-**16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 6.80 (d, 1 H, *J* = 15.4 Hz), 6.44 (d, 1H, *J* = 15.4 Hz), 3.82 (apparent t, 1 H, *J* = 6.6 Hz), 3.65–3.40 (m, 3 H), 2.82 (m, 1 H), 1.94–0.84 (m, 22 H), 1.12 (d, 3 H, *J* = 7.0 Hz), 1.03 (t, 3 H, *J* = 7.4 Hz), 0.91 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 203.5 (s), 154.5 (d), 126.9 (d), 107.9 (s), 85.9 (d), 81.8 (s), 76.2 (d), 66.3 (t), 42.4 (d), 38.3 (d), 36.3 (t), 35.4 (d), 28.0 (q), 26.3 (t), 25.9 (3q), 24.5 (q), 23.1 (t), 18.1 (s), 17.8 (q), 16.1 (q), 12.4 (q), 11.1 (q), -4.1 (q), –4.5 (q); IR(neat): 3460, 1690, 1630 cm^{-1}; MS (EI, 70eV) *m/z* 455 (M-Me, 1), 411(7), 355(8), 263(23), 239(12), 225(13), 213(16), 203(100), 145(33), 123(51), 109(52), 95(46), 75(97); $[\alpha]^{20}_D$ +27.3 (*c* 0.86, $CHCl_3$).