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A Stereoselective Synthesis of the C(8)-C(20) Fragment of Premonensin B

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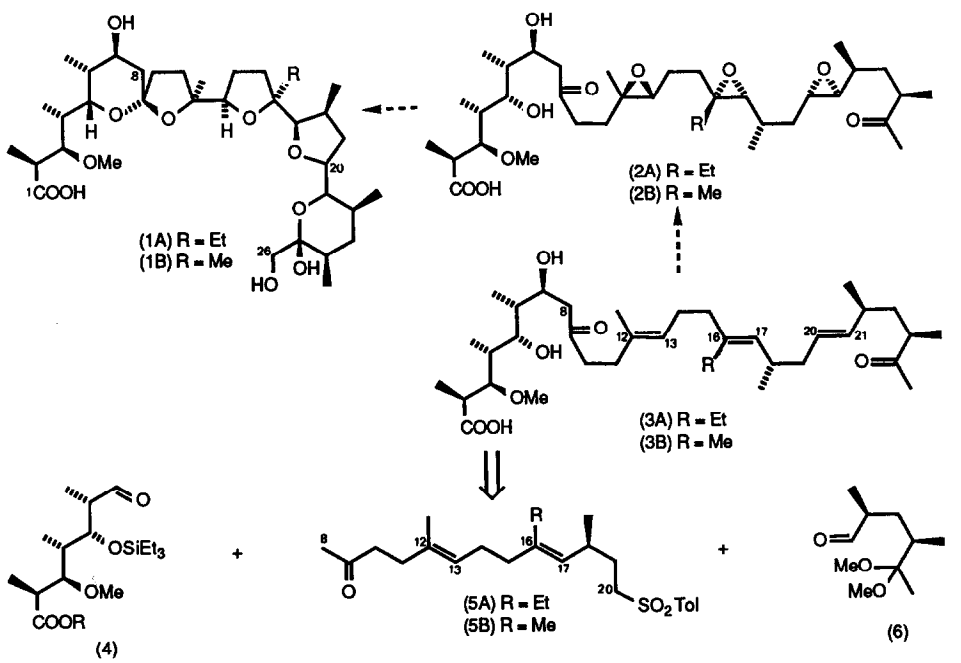
*Abstract. Two stereoselective Ni(0)-catalysed coupling reactions of MeMgBr with cyclic enol ether intermediates were key steps in the synthesis of the C(8)-C(20) fragment (**5B**) of Premonensin B.*

Monensin A (**1A**) and Monensin B (**1B**) are pentacyclic polyether ionophores produced by *Streptomyces cinnamonensis*[1]. In accord with a general scheme of Cane, Celmer, and Westley [2], Cane[3] and Robinson[4] have proposed that (**1A**) and (**1B**) are produced by a complex cascade of ring closures involving the triepoxides (**2A**) and (**2B**) which are derived from the trienes Premonensin A (**3A**) and Premonensin B (**3B**). Recent attempts to illuminate the late stages of Monensin biosynthesis have focused on the total synthesis of the Premonensin trienes[5,6]. We now report a highly stereoselective synthesis of the C(8)-C(20) fragment (**5B**) which, along with the fragments (**4**) and (**6**), constitute key intermediates in a proposed synthesis of Premonensin B[7].



Scheme 1

We recently described a highly stereoselective synthesis of tri-substituted alkenes based on the Ni(0)-catalysed coupling of Grignard reagents with cyclic enol ethers (the Wenkert reaction[8])[9,10]. In the synthesis of the racemic Premonensin B fragment (**5B**) outlined in Scheme 2 we have exploited the remarkable stereoselectivity of this reaction in conjunction with the alkylation of metallated cyclic enol ethers to achieve the stereocontrolled sequential introduction of two new C-C bonds in the construction of the C(12)-C(13) and C(16)-C(17) trisubstituted alkenes (Monensin numbering).

Construction of the C(12)-C(13) alkene was achieved by alkylation of 5-lithio-2,3-dihydrofuran (**7**)[11] with the 3-bromopropan-1-ol derivative (**8**) to give the 5-alkyl-2,3-dihydrofuran (**9**) in 80% yield. Ni(0)-catalysed coupling of the dihydrofuran (**9**) with MeMgBr proceeded rapidly and efficiently with clean retention of stereochemistry to give the homoallylic alcohol (**10**)(82% yield, ≥97% E). Conversion of the alcohol to the primary iodide (**12**) *via* the mesylate was achieved in 97% overall yield.

Construction of the C(16)-C(17) alkene was achieved in an analogous fashion. Alkylation of 6-lithio-3,4-dihydro-2H-pyran (**13**)[12] with the iodide (**12**) gave the 6-alkyl-3,4-dihydropyran (**14**) in only 60% yield owing to competing base-catalysed elimination. The Ni(0)-catalysed coupling of dihydropyran (**14**) with MeMgBr was also less efficient giving the alcohol (**15**) in 57% yield but with high stereoselectivity (≥95%). The diminished yield in the coupling step reflects the much lower reactivity of the dihydropyrans compared with the dihydrofurans[10]. Thus the coupling of MeMgBr with (**14**) required 20h in refluxing benzene and a total of 15 mol% of catalyst (added in three portions) whereas the analogous reaction with dihydrofuran (**9**) required as little as 1 mol% of catalyst and a reaction time of ≤40 min.

To complete the synthesis , the primary alcohol (**15**) was converted to the *p*-tolylsulfone (**18**) in three steps (92% overall yield) using standard reactions. Removal of the *t*-butyl ether protecting group was achieved in modest yield by treating (**18**) with ferric chloride in acetic anhydride followed by methanolysis of the resultant acetate ester[13]. Finally the primary alcohol (**19**) was converted in three steps to the desired racemic Premonensin B fragment (**5B**) as shown in Scheme 2: PMR (270 MHz, $CDCl_3$) 7.77 and 7.36 (2H, each, d, J = 8.3), 5.09 (1H, tq, J = 1.2, 6.9) 4.76 (1H, d, J = 9.5), 3.10-2.90 (2H, m), 2.50 (2H, t, J = 7.3), 2.46 (3h, s,), 2.42-2.30 (1H, m), 2.24 (2H, t, J = 7.5), 2.15 (3H, s), 2.11-1.92 (4H, m), 1.77-1.45 (2H, m), 1.60 (3H, s), 1.54 (3H, d, J = 1.1), 0.91 (3H, d, J = 6.6); CMR (67.5 MHz, $CDCl_3$): 209.0 (s), 144.6 (s), 136.3 (s), 135.7 (s), 133.9 (s), 129.9 (d), 129.0 (d), 128.2 (d), 124.6 (d), 55.0 (t), 42.5 (t), 39.5 (t), 33.6 (t), 31.6 (d), 30.3 (t), 30.0 (q), 26.5 (t), 21.7 (q), 21.3 (q), 21.1 (q), 16.4 (q).

Unfortunately the dihydropyran (**14**) failed to undergo Ni(0)-catalysed coupling with EtMgBr thereby thwarting its application to the synthesis of the Premonensin A fragment (**5A**). Despite this limitation the synthesis reported herein illustrates a new approach to the stereoselective construction of trisubstituted double bonds which should be generally applicable to a wide range of natural products.

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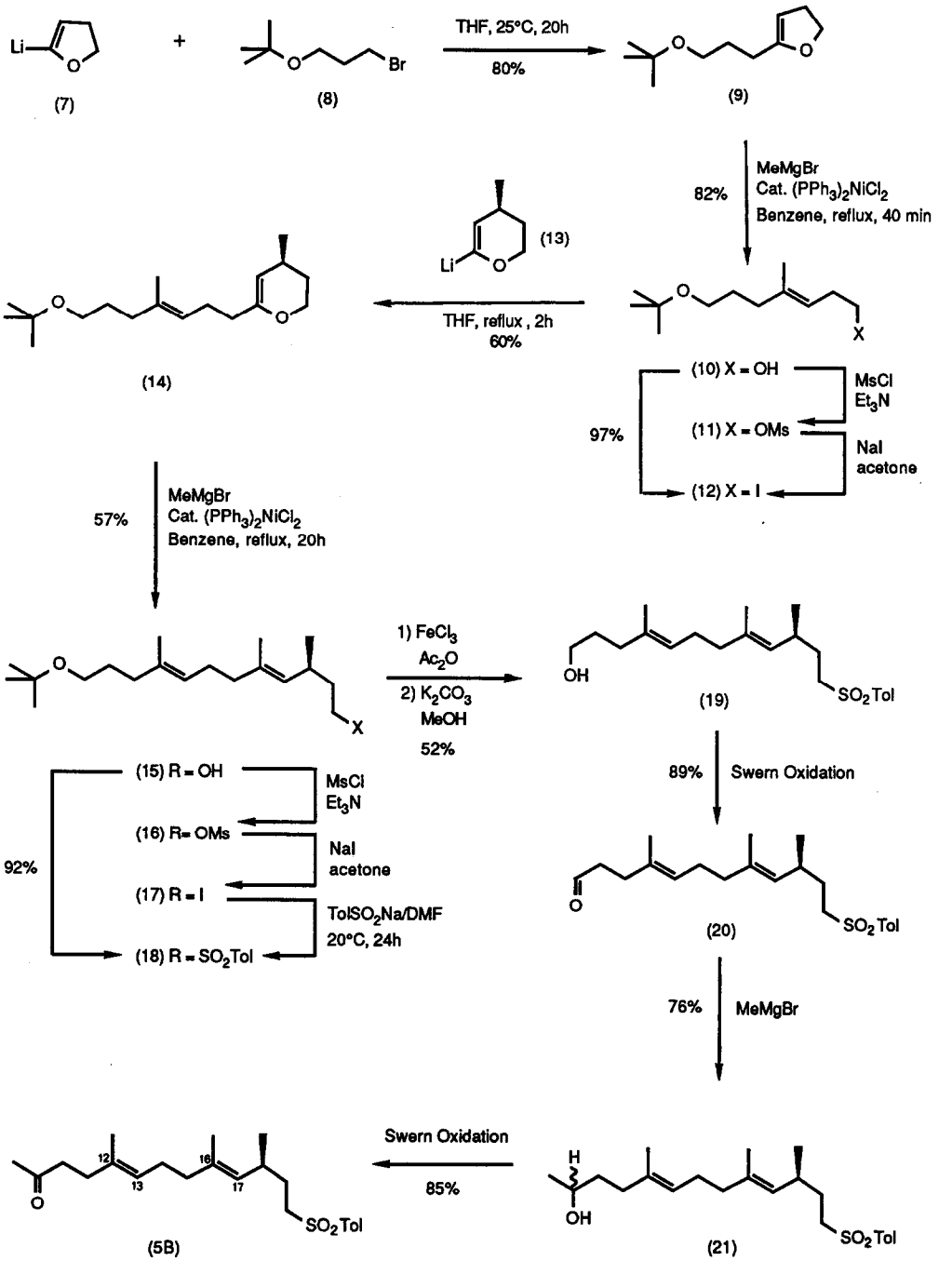
Li
(7)
+
Br
(8)
THF, 25°C, 20h
80%
(9)
82%
MeMgBr
Cat. (PPh3)2NiCl2
Benzene, reflux, 40 min
(13)
Li
THF, reflux, 2h
60%
(14)
(10) X = OH
MsCl
Et3N
97%
(11) X = OMs
NaI
acetone
(12) X = I
57%
MeMgBr
Cat. (PPh3)2NiCl2
Benzene, reflux, 20h
1) FeCl3
Ac2O
2) K2CO3
MeOH
52%
OH
SO2Tol
(19)
89%
Swern Oxidation
(15) R = OH
MsCl
Et3N
(16) R= OMs
NaI
acetone
92%
(17) R = I
TolSO2Na/DMF
20°C, 24h
(18) R = SO2Tol
(20)
76%
MeMgBr
Swern Oxidation
85%
(5B)
(21)

Scheme 2

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14. Spectroscopic data for selected intermediates (PMR at 270 MHz and CMR at 67.5 MHz; $CDCl_3$ used unless otherwise specified): **(9)** PMR (acetone D_6) 4.62 (1H, m), 4.28 (2H, t, J = 6.5), 3.28 (2H, t, J = 6.8), 2.37 (2H, m), 2.07 (2H, m), 1.65-1.58 (2H, m), 1.14 (9H, s); CMR (acetone D_6) 158.6 (s), 93.7 (d), 72.5 (s), 69.8 (t), 60.9 (t), 30.1 (t), 29.9 (t), 28.9 (t), 27.6 (q).

    (10) PMR 5.11 (1H, tq, J = 1.2, 7.3), 3.55 (2H, t, J = 6.0), 3.28 (2H, t, J = 6.6), 2.24 (2H, dt, J = 6.6, 7.2), 2.07 (1H, br s), 2.02 (2H, t, J = 7.6), 1.69-1.55 (2H, m), 1.60 (3H, s), 1.14 (9H, s); CMR 138.1 (s), 119.9 (d), 72.6 (s), 62.3 (t), 61.1 (t), 36.3 (t), 31.5 (t), 28.8 (t), 27.5 (q), 16.1 (q).

    (14) PMR 5.11 (1H, tq, J = 1.3, 7.3), 4.35 (1H, d, J = 2.5), 4.05-3.82 (2H, m), 3.30 (2H, t, J = 6.7), 2.3-1.3 (11H, m), 1.59 (3H, s), 1.17 (9H, s), 0.96 (3H, d, J = 6.7); CMR 153.3 (s), 135.0 (s), 125.6 (d), 123.9 (d), 102.2 (d), 72.5 (s), 64.7 (t), 61.2 (t), 36.2 (t), 34.4 (t), 31.0 (t), 28.8 (t), 27.6 (q), 25.7 (t), 22.3 (q), 16.0 (q).

    (15) PMR 5.09 (1H, tq, J = 1.2, 6.6), 4.91 (1H, dd, J = 1.3, 9.6), 3.59 (2H, m), 3.32 (2H, t, J = 6.8), 2.49 (1H, m), 2.15-1.97 (6H, m), 1.76 (1H, br s), 1.69-1.39 (4H, m), 1.61 and 1.60 (3H each, s), 1.18 (9H, s), 0.94 (3H, d, J = 6.8); CMR 134.8 (s), 134.1 (s), 131.0 (d), 123.9 (d), 72.7 (s), 61.7 (t), 61.4 (t), 40.6 (t), 39.7 (t), 36.1 (t), 29.5 (d), 29.0 (t), 27.6 (q), 26.2 (t), 21.7 (q), 16.2 (q), 16.1 (q).

    Intermediates (9), (10), (14), (15), (18), (19), (20), (21) and (5B) gave satisfactory high resolution mass spectra.

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