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A TOTAL SYNTHESIS OF A NEW TYPE OF FURO[3,2-*h*]ISOQUINOLINE ALKALOID, TMC-120B

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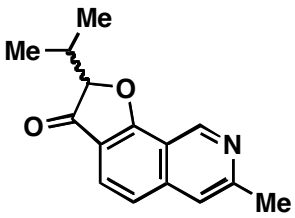
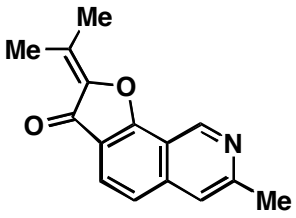
Abstract – A total synthesis of a new furo[3,2-*h*]isoquinoline alkaloid, TMC-120B (**2**) has been completed in sixteen steps. The key step is the synthesis of 7,8-disubstituted isoquinoline (**17**) based on the thermal electrocyclic reaction of 1-azahexatriene system involving the benzene 1,2-bond.

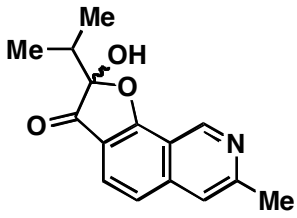
Three new furo[3,2-*h*]isoquinoline alkaloids, TMC-120A (**1**), B (**2**), and C (**3**) were isolated from a fermentation broth of *Aspergillus ustus* TC 1118 (Chart 1).[1] Their structures have been determined by extensive spectroscopic and chemical analyses. TMC-120C (**3**) is the racemic compound, and an absolute configuration of the chiral compound (**1**) has not yet been ascertained. In addition, the structure of TMC-120B (**2**) has been also elucidated by X-Ray analysis. TMC-120B (**2**) shows moderate inhibitory activity against the interleukin-5 mediated prolongation of eosinophil survival (IC_{50}=2.0□M).



1 : TMC-120A



2 : TMC-120B

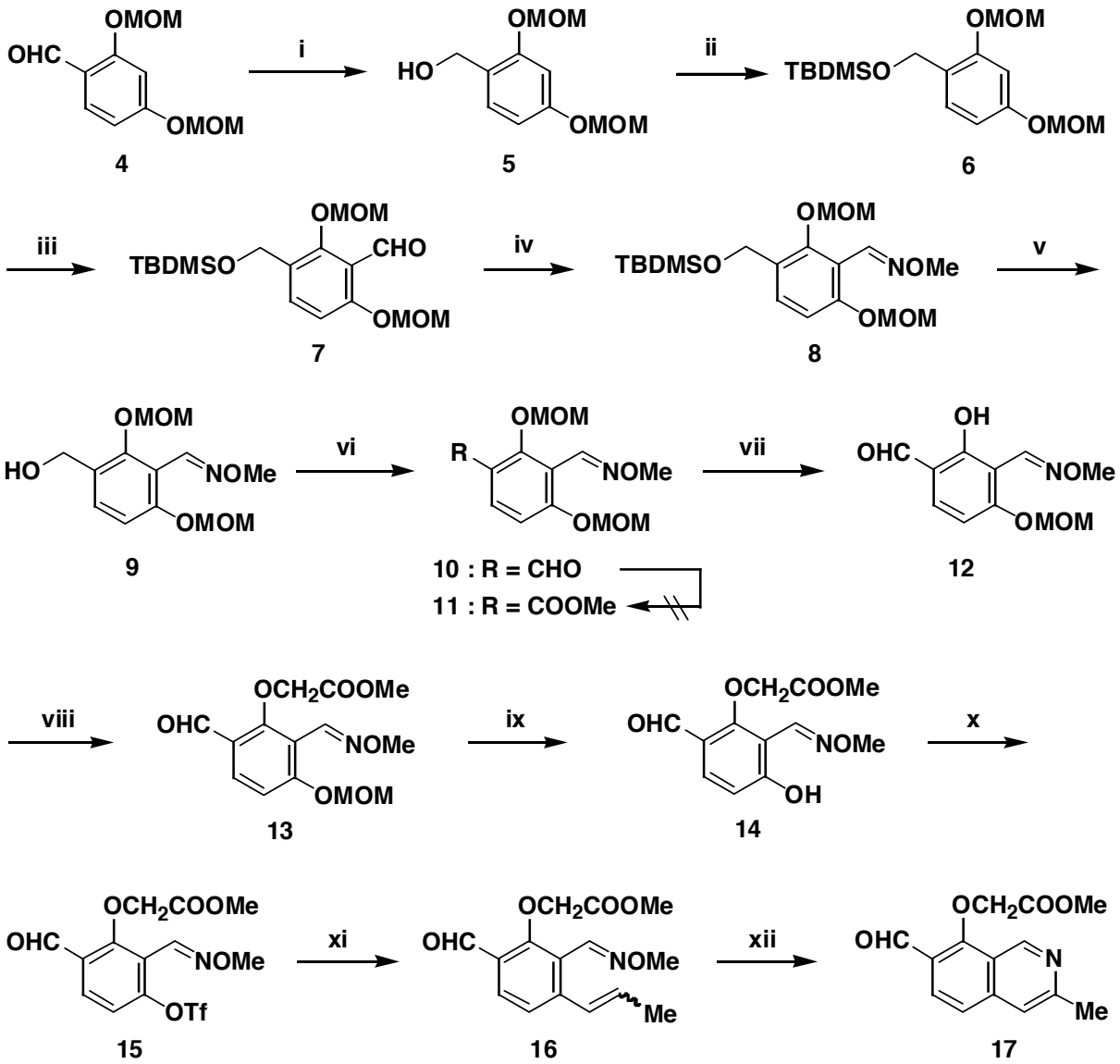


3 : TMC-120C

Chart 1

We have been performing synthetic studies of biologically active condensed heteroaromatic compounds including natural products through the construction of functionalized frameworks based on the thermal electrocyclic reaction[2] of either a 6□-electron[3,4] or an aza 6□-electron[3,5] system incorporating the heteroaromatic or aromatic portion. In our research program, we planned a total synthesis of TMC-120A (**1**), B (**2**), and C (**3**).

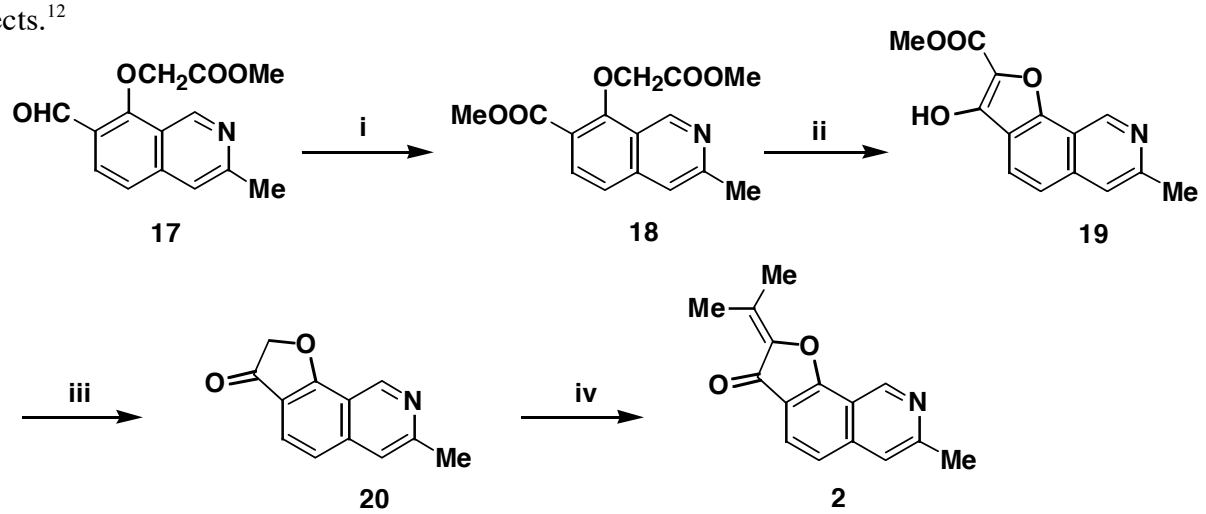
In this paper, we here describe the first total synthesis of TMC-120B (**2**) through the synthesis of 7,8-disubstituted isoquinoline nucleus by an application of an aza 6π-electrocyclic reaction[3,4] of a 1-azahexatriene system, involving the benzene 1,2-bond. We chose the known 2,4-dimethoxymethyl(di-MOM)oxybenzaldehyde (**4**)[6] as a starting material. As shown in Scheme 1, reduction of benzaldehyde (**4**) with sodium borohydride in EtOH, followed by treatment of the resulting alcohol (**5**: 90%)[7] with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole in DMF gave the TBDMS ether (**6**) (85%). The ether (**6**) was treated with *n*-BuLi in THF, and the resulting lithio compound[8] was then



Scheme 1. Reagent and conditions : (i) $NaBH_4$, EtOH, rt, 2 h (90%), (ii) TBDMSCl, imidazole, DMF, rt, 12 h (85%), (iii) *n*-BuLi, THF, 40 min and then DMF, 0°C, 20 min (75%), (iv) $MeONH_2 \cdot HCl$, AcONa, EtOH, 80°C, 12 h (89%), (v) TBAF, THF, rt, 1.5 h (92%), (vi) act. MnO_2, CH_2Cl_2, rt, 24 h (89%), (vii) conc. HCl, MeOH, 0°C, 3 h (92%), (viii) NaH, DMF, $BrCH_2COOMe$, rt, 12 h (93%), (ix) AcOH, 90°C, 12 h (80%), (x) Tf_2O, pyridine, CH_2Cl_2, 0°C, 4 h (85%), (xi) Me-CH=CH-$SnBu_3$, Et_4NCl, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 4 h (83%), (xii) 180°C, *o*-dichlorobenzene, 30 min (44%).

quenched with DMF to yield the benzaldehyde derivative (**7**) (75%). The reaction of the aldehyde (**7**) tetrabutylammonium fluoride (TBAF) in THF to give benzyl alcohol (**9**) (92%). Oxidation of **9** with with hydroxylamine methyl ether in EtOH gave oxime methyl ether (**8**) (89%), which was treated with activated manganese dioxide (MnO_2) in CH_2Cl_2 afforded the benzaldehyde derivative (**10**) (89%), but a direct conversion of a formyl group of **10** into the methyl ester (**11**) failed. On the other hand, treatment of **10** with conc. HCl in MeOH at 0°C selectively produced 2-hydroxybenzaldehyde derivative (**12**) (92%), which was converted into the ether (**13**) by means of methyl bromoacetate with sodium hydride (93%). The cleavage of MOM-ether (**13**) in acetic acid at 90°C successfully provided the 4-hydroxybenzaldehyde (**14**) (80%), and sequential treatment of **14** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine at 0°C then gave the triflate (**15**) (85%). The palladium-catalyzed cross-coupling reaction of **15** with tributyl 1-propenyltin in the presence of $PdCl_2(PPh_3)_2$ in DMF at 80°C afforded the appropriate *o*-propenyl aldoxime methyl ether (**16**) (83%) as a 1-aza 6π-electron system. The thermal electrocyclic reaction of **16** was carried out in *o*-dichlorobenzene at 180°C[3,5] to produce the desired 7,8-disubstituted isoquinoline (**17**) in a somewhat low yield (44%).

For the formation of the furanone ring by Dieckmann condensation (Scheme 2), 7-formylisoquinoline (**17**) was converted into the methyl ester (**18**) using sodium cyanide, MnO_2, and acetic acid in MeOH according to Corey's procedure[9] (83%). The cyclization of **18** with sodium methoxide in MeOH at 80°C gave the β-keto ester (**19**) (66%), which was treated with lithium hydroxide in aqueous DMSO at 70°C[10] to yield the expected furanone (**20**) (75%). Finally, the reaction of **20** with acetone in the presence of lithium diisopropylamide (LDA), followed by treatment with methanesulfonyl chloride (MsCl) and dimethylaminopyridine (DMAP) in pyridine[11] provided TMC-120B (**2**) (33%). The physical and spectroscopic data of synthetic TMC-120B (**2**) agreed with those of natural TMC-120B (**2**) in all respects.[12]



Scheme 2. Reagent and conditions : (i) NaCN, AcOH, MnO_2, MeOH, rt, 4 h (83%), (ii) NaOEt, MeOH, 80°C, 12 h (66%), (iii) LiOH · H_2O, DMSO-H_2O, 70°C, 2 h (75%), (iv) LDA, Me_2CO, THF, -78°C, 4 h; $MeSO_2Cl$, DMAP, pyridine, 0°C, 2 h (33%).

Thus, a first total synthesis of TMC-120B (**2**) was completed in sixteen steps through the construction of the appropriate 7,8-disubstituted isoquinoline framework based on the thermal electrocyclic reaction of the 1-azatriene system, followed by the formation of a furanone ring. Further studies of the total syntheses of TMC-120A (**1**) and C (**3**) are now in progress.

ACKNOWLEDGEMENT

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12. Synthetic TMC-120B (**2**): mp 175-178ºC (MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) □ 2.26 (3H, s), 2.45 (3H, s), 2.76 (3H, s), 7.38 (1H, d, *J*=8.6 Hz), 7.56 (1H, s), 7.83 (1H, d, *J*=8.6 Hz), 9.57 (1H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) □ 17.6, 20.4, 24.7, 114.6, 119.4, 119.6, 120.6, 124.2, 133.9, 141.4, 145.6, 146.2, 156.7, 164.0, 182.3. Natural TMC-120B (**2**): mp 176-177ºC; ^{1}H-NMR (400 MHz, $CDCl_3$) d 2.25 (3H, d, *J*=0.7 Hz), 2.43 (3H, d, *J*=0.7 Hz), 2.74 (3H, s), 7.35 (1H, d, *J*=8.5 Hz), 7.52 (1H, s), 7.80 (1H, d, *J*=8.5 Hz), 9.52 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) □ 17.5, 20.4, 24.7, 114.6, 119.3, 119.5, 120.5, 124.1, 133.7, 141.3, 145.6, 146.2, 156.7, 164.0, 182.1.