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). 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 \mu M).

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 of either a 6π-electron or an aza 6π-electron 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 (TBDMSCI) 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 reduced with sodium cyanoborohydride in THF to give hydroxy compound (7).

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\begin{align*}
4 & \xrightarrow{i} 5 & 6 \\
& \xrightarrow{ii} 7 & 8 \\
& \xrightarrow{iii} 9 & 10: R = \text{CHO} \\
& & 11: R = \text{COOMe} \\
& \xrightarrow{iv} 12 & 13 \\
& \xrightarrow{v} 14 & 15 \\
& \xrightarrow{vi} 16 & 17 \\
& \xrightarrow{vii} 18 & 19 \\
& \xrightarrow{viii} 20 & 21 \\
& \xrightarrow{ix} 22 & 23 \\
& \xrightarrow{x} 24 & 25 \\
& \xrightarrow{xi} 26 & 27 \\
& \xrightarrow{xii} 28 & 29 \\
\end{align*}
\]

Scheme 1. Reagent and conditions: (i) NaBH\(_4\), EtOH, rt, 2 h (90%), (ii) TBDMSCI, imidazole, DMF, rt, 12 h (85%), (iii) \(n\)-BuLi, THF, 40 min and then DMF, 0°C, 20 min (75%), (iv) MeONH\(_2\) - HCl, AcONa, EtOH, 80°C, 12 h (89%), (v) TBAF, THF, rt, 1.5 h (92%), (vi) act. MnO\(_2\), CH\(_2\)Cl\(_2\), rt, 24 h (89%), (vii) conc. HCl, MeOH, 0°C, 3 h (92%), (viii) NaH, DMF, BrCH\(_2\)COOMe, rt, 12 h (93%), (ix) AcOH, 90°C, 12 h (80%), (x) Tf\(_2\)O, pyridine, CH\(_2\)Cl\(_2\), 0°C, 4 h (85%), (xi) Me-CH=CH-SnBu\(_3\), Et\(_4\)NCl, PdCl\(_2\)(PPh\(_3\))\(_2\), DMF, 80°C, 4 h (83%).
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 hydroxylamine methyl ether in EtOH gave oxime methyl ether (8) (89%), which was treated with activated manganese dioxide (MnO₂) in CH₂Cl₂ 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 (Tf₂O) 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 PdCl₂(PPh₃)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°C⁵ 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, MnO₂, and acetic acid in MeOH according to Corey’s procedure⁹ (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°C¹⁰ 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 pyridine¹¹ 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, MnO₂, MeOH, rt, 4 h (83%), (ii) NaOEt, MeOH, 80°C, 12 h (66%), (iii) LiOH - H₂O, DMSO-H₂O, 70°C, 2 h (75%), (iv) LDA, Me₂CO, THF, -78°C, 4 h; MeSO₂Cl, 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.

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REFERENCES AND NOTES


7. All new compounds provided satisfactory spectroscopic and analytical data.


12. Synthetic TMC-120B (2): mp 175-178°C (MeOH); $^1$H-NMR (300 MHz, CDCl$_3$) δ 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$_3$) δ 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 176-177°C; $^1$H-NMR (400 MHz, CDCl$_3$) δ 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$_3$) δ 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.