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First total synthesis of topopyrone C

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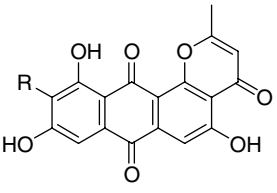
Abstract—The first synthesis of topopyrone C, a natural compound and inhibitor of Topoisomerase I, has been carried out by Marschalk alkylation of 1-hydroxy-3,6,8-trimethoxyanthraquinone, followed by a Baker–Venkataraman chain elongation and an acid-catalyzed cyclization for the construction of the pyrone ring.

Nature continues to be an important source of new biologically active compounds. Many useful drugs are of natural origin, or are obtained by skilful modification of natural substances.[1] We are interested in potential inhibitors of topoisomerase I, an ubiquitous enzyme that plays an important role in DNA replication, transcription, recombination, and repair.[2] Inhibition of topoisomerase I can have important consequences for chemotherapic treatment of tumors.[3]

Human topoisomerase I (top1) is the molecular target of a diverse set of anticancer compounds, including camptothecins,[4] indolocarbazoles, and indenoisoquinolines.[5] These compounds bind to a transient top1-DNA covalent complex and inhibit the resealing of a single-strand break that the enzyme creates to relieve superhelical tension in the duplex DNA.[6] Other compounds, however, that differ from camptothecins, can inhibit topoisomerase I through an alternative mechanism,[5] such as inhibition of the catalytic site.

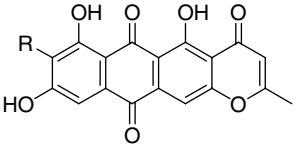
Recently, Kanai et al.[7] have discovered four new specific inhibitors of topoisomerase I, topopyrones A–D (**1**–**4**).

All four compounds were isolated from the culture broth of a fungus, *Phoma* sp. BAUA2861, as well as two of them from *Penicillium* sp. BAUA4206. Structural elucidation showed that these compounds are of anthraquinone type, containing a fused 1,4-pyrone moiety.[8]



1 Topopyrone A R=Cl

2 Topopyrone C R=H



3 Topopyrone B R=Cl

4 Topopyrone D R=H

Topopyrones A, B, C, and D selectively inhibit recombinant yeast growth, depending on the expression of human topoisomerase I. All these compounds showed significant cytotoxic effects (in the range 0.7–20 μM) against a panel of tumor cell lines when tested in vitro.[7]

Herein, we would like to disclose a route to the synthesis of topopyrones which may also be amenable to the synthesis of new derivatives. Our aim was to make these compounds available for biological testing and for the investigation of the structural requirements for antitumor activity.

The synthetic approach was based on the use of the Marschalk alkylation reaction of 1-hydroxy-3,6,8-trimethoxyanthraquinone[9] followed by a Baker–Venkataraman chain elongation[10] and an acid-catalyzed cyclization for the construction of the pyrone framework.

The formation of 1-hydroxy-3,6,8-trimethoxyanthraquinone was initially envisioned to proceed through two subsequent Diels–Alder cycloadditions of Brassard diene (**6**)[11] onto the commercially available 2,6-dichloro-1,4-benzoquinone (Scheme 1).

Keywords: Topopyrone C; Synthesis; Anthraquinone; Topoisomerase; Marschalk reaction.
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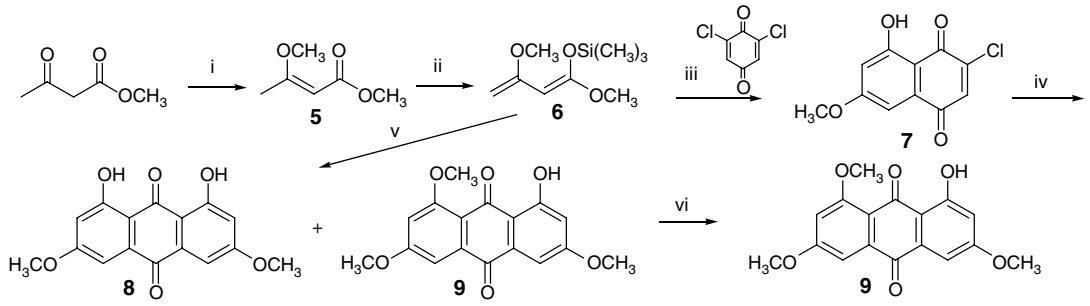


Scheme 1. Reagents and conditions: (i) $CH(OCH_3)_3$, H_2SO_4, rt, 24 h, 88%; (ii) LDA, TMSCl, THF, −78 °C, 45 min, then 20 °C, 3 h, 100%; (iii) (1) THF, −30 °C, 30 min, then rt, 1 h; (2) silica gel, CH_2Cl_2, 1 day, 82%; (iv) (1) **6**, THF, rt, 2.5 h; (2) silica gel, CH_2Cl_2, 3 days; (v) (1) 2,6-dichlorobenzoquinone, THF, −78 °C then rt, 2 h; (2) 130 °C, 10 h; (3) MeOH/HCl 10% 3:1 reflux, 30 min.; (vi) $TsOCH_3$, Na_2CO_3, tetraglyme, 140 °C, 2 h, overall yield from **7**: 42%; overall yield via route v: 40%.

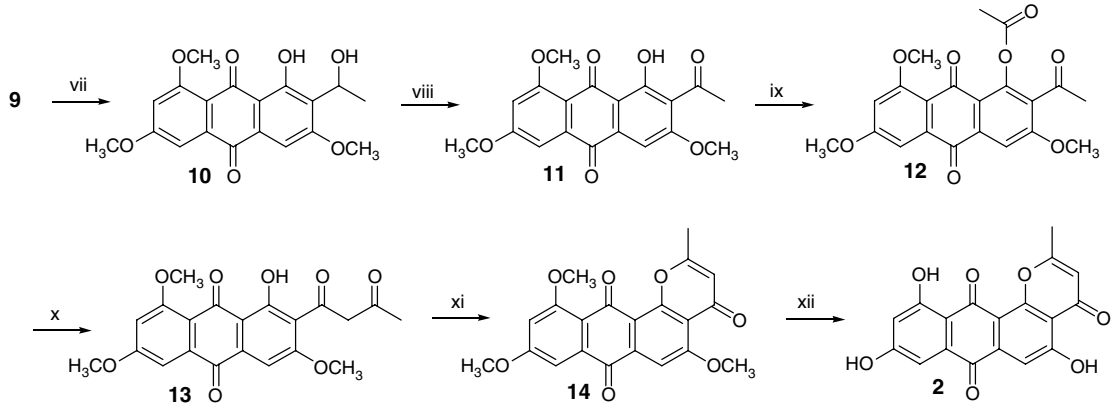
The first cycloaddition reaction, done at −30 °C, between 2,6-dichloro-1,4-benzoquinone and **6** gave the naphthoquinone **7** as the major product, after a rather cumbersome aromatization process, which required 24 hours of stirring with a large amount of deactivated[12] silica gel. The second Diels–Alder reaction, done at room temperature, afforded a nonseparable mixture of anthraquinones **8** and **9**.

We then found that this procedure could be greatly simplified by employing an excess of diene **6** to directly obtain the mixture of **8** and **9** after pyrolysis, at 130 °C for 10 h[13] (Scheme 1, step v), without isolating the intermediate naphthoquinone. This mixture was then converted into 1-hydroxy-3,6,8-trimethoxyanthraquinone **9** with methyl *para*-toluenesulfonate in tetraglyme at 140 °C,[14] with an overall yield of 40% from 2,6-dichloro-1,4-benzoquinone. Interestingly, this procedure proved to be very selective, exclusively producing the 1-hydroxy product.[15]

Reduction of **9** with sodium dithionite under basic conditions gave 1-hydroxy-3,6,8-trimethoxy-9,10-dihydroanthraquinone, which was alkylated in situ with acetaldehyde in the *ortho* position, relative to the phenolic hydroxy group, and rapidly re-oxidized to quinone **10** (30%) using hydrogen peroxide in an alkaline reaction medium.[9c] Purification of this and of the following crude products required flash column chromatography using silica gel previously deactivated with KH_2PO_4. Oxidation of **10** to ketone **11** was first performed using pyridinium chlorochromate, as described by Krohn and Vitz,[9c] with a 43% yield. We tried to improve the process by using different oxidants and we found that a PCC catalyzed (2 mol %) oxidation, using 1.05 equiv of H_5IO_6 in acetonitrile,[16] gave the desired ketone in a 60% yield.[17] (Scheme 2).

The phenolic hydroxy group was then acetylated with acetic anhydride to give **12** (88%). The subsequent intramolecular acylation was initiated by LiH in boiling THF to afford compound **13** in a 55% yield. The last step of the synthesis was an acid-catalyzed cyclization, that was achieved by simply dissolving phenolic β-diketone **13** in trifluoroacetic acid to obtain tri-*O*-methyltopopyrone C **14** (76%).

The pyranone ring was probably formed by a reversible hemiketal formation, involving the phenolic group and the 3′-oxo group, followed by an irreversible water elimination step. Demethylation of **14** with boron tribromide afforded Topopyrone C **2** whose spectroscopic data were consistent with the structure of the natural compound.[18]



Scheme 2. Reagents and conditions: (vii) (1) NaOH, $Na_2S_2O_4$, CH_3OH, 0 °C; (2) CH_3CHO, 20 °C, 3 h; (3) H_2O_2, 0 °C, 30%; (viii) PCC, H_5IO_6, CH_3CN, 0 °C, 30 min, then rt, 3 h, 60%; (ix) Ac_2O, Py, reflux, 10 h, 88%; (x) LiH, THF, reflux, 20 h, 55%; (xi) CF_3COOH, 0 °C, 20 min, rt, 10 min, 76%; (xii) BBr_3, CH_2Cl, −60 °C, 90 min, 25%.

When this work was already completed, a different approach to the synthesis of Topopyrones B and D was reported by Tan and Ciufolini.[19]

Acknowledgment

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Supplementary data

Experimental procedure and characterization data for compounds **10**,**12**–**14** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.164.

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12. Procedure for preparing deactivated silica gel: 110 g of silica gel were suspended in 400 mL of 4% KH_2PO_4. After evaporation of water, silica was dried in the oven overnight.
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15. *Synthesis of 1-hydroxy-3,6,8-trimethoxyanthraquinone* **9**: A solution of (1,3-dimethoxy-buta-1,3-dienyloxy)trimethylsilane (8.8 g, 43.9 mmol) in dry THF (16 mL) was added dropwise at −78 °C to a solution of 2,6-dichloro-1,4-benzoquinone (2.59 g, 14.6 mmol) in dry THF (26 mL). The mixture was allowed to warm at room temperature, stirred for 2 h, and then evaporated. The crude product was pyrolyzed at 130 °C for 10 h. A solution of 3:1 MeOH/10% HCl (aq) was added to the residue and the mixture was refluxed for 0.5 h, cooled, diluted with water, and filtered. The solid was taken up with AcOEt and filtered. The residue was extracted in a Soxhlet apparatus with CH_2Cl_2 and the two organic phases were joined, dried, and evaporated to give 1.98 g of a mixture of 1,8-dihydroxy-3,6-dimethoxyanthraquinone (**8**) and 1-hydroxy-3,6,8-trimethoxyanthraquinone (**9**). Without further purification, the crude products were heated at 140 °C in tetraglyme (74 mL) with Na_2CO_3 (1.05 g, 9.89 mmol) and methyl tosylate (1.9 mL, 13.18 mmol) for 2 h. The mixture was cooled, diluted with water (250 mL), and filtered. The orange solid was purified by flash chromatography (Et_2O/CH_2Cl_2) to give 1.84 g of 1-hydroxy-3,6,8-trimethoxyanthraquinone (**9**) (40%); mp 255–256 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (3H, s, –OMe), 3.98 (3H, s, –OMe), 4.02 (3H, s, –OMe), 6.69 (1H, d, 1Ar, $J = 2.61$ Hz), 6.80 (1H, d, 1Ar, $J = 2.61$ Hz), 7.29 (1H, d, 1Ar, $J = 2.61$ Hz), 7.45 (1H, d, 1Ar, $J = 2.61$ Hz), 13.38 (1H, s, –OH).
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17. *Oxidation*: A solution of periodic acid (200 mg, 0.88 mmol) in 6.6 mL of acetonitrile was stirred at room temperature for 15 min. After cooling at 0 °C, 300 mg of **10** (0.84 mmol) and 10 mg of PCC in acetonitrile (1.6 mL) were added. The solution was stirred at 0 °C for 30 min, then at room temperature for 3 h. The reaction mixture was then diluted with dichloromethane and washed with 1:1 brine:water, saturated aq Na_2SO_3 olution, and brine, respectively, dried over anhydrous Na_2SO_4, and concentrated to give the crude ketone. Purification by flash chromatography (CH_2Cl_2/acetone 97:3) afforded pure 2-acetyl-1-hydroxy-3,6,8-trimethoxyanthraquinone **11** (180 mg, 60%); mp 216–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.55 (3H, s, MeCO), 3.97 (3H, s, –OMe), 3.99 (3H, s, –OMe), 4.02 (3H, s, –OMe), 6.80 (1H, d, 1Ar, $J = 2.61$ Hz), 7.32 (1H, s, 1Ar), 7.45 (1H, d, 1Ar, $J = 2.61$ Hz), 13.48 (1H, s, –OH).
18. Topopyrone C: Compound **14** (20 mg, 0.05 mmol) was dissolved in dry dichloromethane under nitrogen. After cooling at −60 °C, BBr_3 was added (0.08 mL, 0.78 mmol) and the mixture was stirred for 30 min, then allowed to stand at room temperature. Water was added, the two layers were separated and the aqueous phase was extracted with dichloromethane, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel deactivated with KH_2PO_4 (acetone/dichloromethane 2:8) to give Topopyrone C (**2**) (4 mg, 25%); mp > 250 °C, ^{1}H NMR (300 MHz, acetone-d_6) δ: 2.58 (3H, s, Me), 6.47 (1H, s, CH=), 6.67 (1H, d, 1Ar, $J = 2.24$ Hz), 7.18 (1H, d, 1Ar, $J = 2.24$ Hz), 7.43 (1H, s, 1Ar), 13.16 (1H, s, –OH), 14.11 (1H, s, –OH); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.55 (3H, s, Me), 6.62 (1H, s, CH=), 6.64 (1H, d, 1Ar, $J = 2.20$ Hz), 7.10 (1H, d, 1Ar, $J = 2.20$ Hz), 7.40 (1H, s, 1Ar), 11.30 (1H, s, –OH), 13.15 (1H, s, –OH), 14.18 (1H, s, –OH); HRMS/ESI negative: calcd for $C_{18}H_9O_7$ 337.03538, found 337.03529 $[M-H]^-$; calcd for $C_{18}H_8O_7Na$ 359.01732, found 359.01769 $[M-2H+Na]^-$; calcd for $C_{36}H_{18}O_{14}Na$ 697.05997, found 697.061378 $[2M-2H+Na]^-$.
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