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A Facile Route to Stereoselective Synthesis of *Exo*-4, 5-epoxytricyclo[6.2.1.$0^{2,7}$]undeca-9-ene-3,6-diol as a Valuable Intermediate to Conduritol-F Natural Product

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Tricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-diol (**2**) was prepared from readily available tricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-dione and was transformed in an entirely new and convenient route to *exo*-4,5-epoxytricyclo[6.2.1.$0^{2,7}$]undeca-9-ene-3,6-diol (**5**) as a valuable intermediate to the synthesis of conduritol-F.

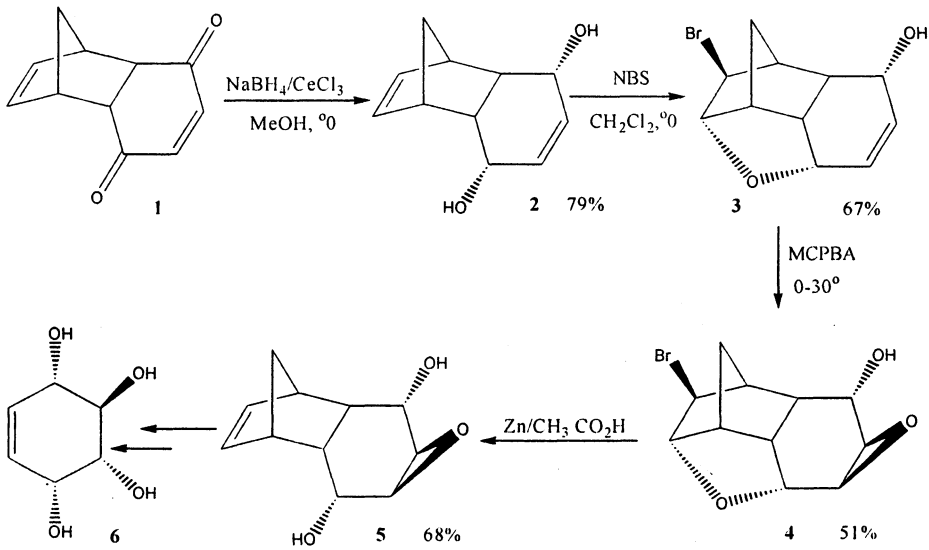
Key Words: Conduritols, Stereoselective, Natural product, Conduritol-F.

INTRODUCTION

Polyhydroxylated cyclohexene derivatives are useful synthons and more often possess diverse biological activities[1]. They have been used as useful intermediates for the synthesis of conduritols, epoxides, cyclitols, aminocyclitols, aminoconduritols and cyclophellitols[2]. As a result, stereo controlled syntheses of conduritols and their derivatives have attracted a great deal of attention recently. For example, enantiomerically pure (+)-conduritol-B and (–)-conduritol-F derivatives have been synthesized, starting from D-mannitol and D-sorbitol, respectively. The modified method has also been used for the synthesis of unprotected conduritols[3] namely (–)-conduritol-E and (–)-conduritol-F. The ring closing metathesis (RCM) has been employed for the synthesis of di-O-methyl derivative of conduritol-E in enantiomerically pure form starting from diethyl L-tartrate[4]. In a recent report the same methodology (RCM) was employed for the preparation of condutritol-A, E and F derivatives using galacitol, D-mannitol and D-glucitol, respectively as starting materials; the key steps of this approach comprise a Tebbe olefination reaction for the preparation of the required dienes followed by ring closing metathesis for the formation of the polyhydroxylated cyclohexene rings of the targets[5]. Interestingly, Chung and his coworker[6] have reported the first synthesis of all possible enantiomeric pairs of conduritol stereo isomers by an efficient enzymatic resolution of conduritol-B and C derivatives, followed by oxidation/reduction and Mitsunobu reaction in stereo- and regioselective manners.

RESULTS AND DISCUSSION

In continuation of our studies for the preparation of optically active functionalized norbornane derivatives with the aim of their utilization as chiron in biologically interesting products[7], the main objective was to design a new synthetic route for the preparation of *exo*-4,5-epoxytricyclo[6.2.1.0^{2,7}]undeca-9-ene-3,6-diol (**5**) as a valuable intermediate to conduritol-F. In this respect, the synthetic strategy depicted in **Scheme-1** was proposed.

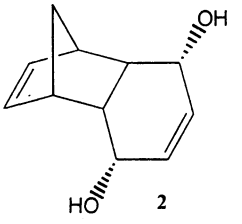


Scheme-1

Cycloadduct **1** was prepared by using Diels-Alder methodology[8]. Stereoselective reduction of cycloadduct **1** using $NaBH_4$ in the presence of $MgCl_2$ and $CeCl_3$ in MeOH was investigated. The reduction in the presence of $MgCl_2$ gave a mixture of stereo isomers (**2** and **2a**, ratio 2 : 1 by ^1H NMR). AM-1 calculations showed that *endo-endo* diol (**2**) is more stable than the *endo-exo* (**2a**) and *exo-exo* (**2b**) isomers; no trace of the last one could be detected in this experiment. Treatment of **1** with sodium borohydride in the presence of $CeCl_3$ afforded a completely stereoselective reduction *meso*-3,6-diol (**2**) in 79% yield, m.p. = 156.5–157°C (m.p. = 157–158°C).[9]

In the compound **2** one of the *endo* hydroxy groups was protected by using NBS in CH_2Cl_2 at 0°C which produced bromo ether (**3**) in 67% yield. Epoxidation of **3** with *m*-chloroperbenzoic acid (*m*-CPBA) gave *exo*-epoxide **4** as colourless crystals (from petroleum ether : dichloromethane 3 : 1) in 51% yield, m.p. = 125–126°C. Zn/CH_3CO_2H reduction of epoxyether (**4**) at room temperature cleanly furnished *meso*-3,6-diol epoxide **5** in 68% yield as a crystalline solid, m.p. = 128–129°C. This product is a useful precursor for the conduritol-F (**6**) and can be converted to this valuable natural product using thermal cycloreversion

techniques[10] followed by epoxide ring opening. The structures of all products were confirmed by spectroscopic methods.



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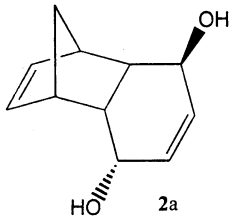
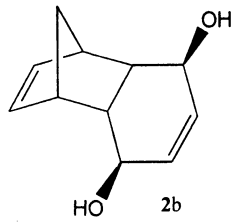


2a



2b

In conclusion, we have described the syntheses outlined in **Scheme 1** which formally represent a new approach to the preparation of naturally occurring conduritol-F **(6)** from the readily available adduct **1**.

EXPERIMENTAL

Chemicals were purchased from Merck and Fluka. Melting points were measured with Electro Thermal and are uncorrected. IR spectra were determined on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC, FT-NMR (80 MHz) in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS). Mass spectra were measured on Shimadzu GCMS-QP1100EX. Preparative thin layer chromatography prepared from Merck Kieselgel 60 H, F_{254}, Art No 7730. GC was carried out using Buck Scientific 910 (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-diol (2)

Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (3.5 g, 20 mmol) (prepared from *p*-benzoquinone and freshly distilled cyclopentadiene) was added to a solution of $CeCl_3 \cdot 7H_2O$ (15.0 g, 40.0 mmol) in methanol (60 mL). The solution was cooled in a salt-ice bath and $NaBH_4$ (1.5 g, 40 mmol) was added in portions and the temparature was kept under 0°C. The progress of the reaction was monitored by TLC. The reaction was completed in 5 min. The mixture was treated with water and the aqueous solution was extracted with $CHCl_3$ (4 × 30 mL). The organic phase was dried ($MgSO_4$), evaporated under vacuum and the residue was recrystallized from acetone to produce tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-diol **(2)** (2.82 g, 15.9 mmol) in 79% yield, as white crystals, m.p. = 156.5–157°C (lit. m.p. = 157–158°C)[9]. IR (ν_{max}) (KBr), 3300 (vs), 2980–2800 (s), 3020 (m), 1640 (w), 1350 (s), 1050 (vs), 710 (vs) cm^{-1}; ^{1}H NMR (pyridine): δ 5.72 (2H, t, J = 2 Hz), 5.3 (2H, s), 4.3 (2H, m), 4.15 (2H, br s), 2.9 (2H, m), 2.6 (2H, m), 1.2 (2H, m) ppm.

11-Bromo-2-oxatetracyclo[6.2.1.1^{3,10}.0^{7,12}]dodeca-4-ene-6-ol (3)

To an ice-cooled magnetically stirred solution of tricyclo [6.2.1.0^{2,7}] undeca-4, 9-dione-3,6-diol (4.45 g, 25 mmol) in CH_2Cl_2 (60 mL), N-bromosuccinimide

(NBS) (4.65 g, 26.5 mmol) was added and stirring continued at this temperature for 4 h. The progress of the reaction was monitored by TLC. Petroleum ether (b.p. = 30–50°C) (50 mL) was added and the mixture was filtered. To the filtrate sodium acetate (25 mg) was added and filtered. The solvent was evaporated under vacuum without applying the heat to furnish the desired bromo ether **(3)** (4.3 g, 16.7 mmol) in 67% yield as colourless crystals, recrystallized successively from petroleum ether : dichloromethane (3 : 1) and carbon tetrachloride, m.p. = 125–126°C. IR (ν_{max}) (KBr): 3300 (vs), 3020 (w), 2850–2970 (s), 1640 (w), 1040 (vs), 1020 (s), 960 (s), 920 (vs), 900 (s), 635 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.8 (2H, m), 4.5 (2H, d, J = 5 Hz), 4.3 (1H, m), 4.15 (1H, d, J = 2 Hz), 1.3–3 (7H, m) ppm; MS: m/e (%), 258 (M + 2, 10.0), 256 (M^+, 10.0), 241 (57.0), 239 (58.0), 177 (74.0), 159 (83.0), 91 (83.0), 39 (64.0).

11-Bromo-2-oxa-*exo*-epoxy-4,5-tetracyclo[6.2.1.$1^{3,10}$.$0^{7,12}$]dodeca-6-ol (4)

To a stirred solution of bromoether **3** (2.57 g, 10 mmol) in CH_2Cl_2 (20 mL), saturated aqueous solution of Na_2CO_3 (20 mL) was added until pH = 8 at 0°C. A solution of *m*-chloroperbenzoic acid (3.4 g, 10 mmol, 50% solution) in CH_2Cl_2 (20 mL) was added dropwise in 1 h and the temperature of the reaction mixture was gradually raised to 28°C and stirred at this temperature for 24 h. The reaction mixture was washed by an aqueous solution of Na_2SO_3, NaCl and water. The organic phase was dried and evaporated under vacuum to produce a solid residue which was recrystallized from petroleum ether (b.p. = 40–60°C) to provide the desired bromo epoxide **4** (1.39 g, 5.1 mmol) in 51% yield. IR (ν_{max}) (KBr) : 3280 (s), 2950 (m), 2800 (m), 1265 (m), 1040 (vs), 970 (s), 895 (s), 860 (w), 635 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.2–4.8 (4H, m), 3.2–3.8 (2H, m), 2.4–3.1 (5H, m), 1.4–2.0 (2H, m) ppm; MS : m/e (%), 274 (M + 2, 2.86), 272 (M^+, 2.86), 256 (10.5), 258 (10.5), 239 (31.4), 241 (31.4), 177 (100.0).

***Exo*-4,5-epoxytricyclo[6.2.1.$0^{2,7}$]undeca-9-ene-3,6-diol (5)**

Zn (0.24 g) was gradually added to a stirred solution of epoxyether **4** in glacial acetic acid (2.0 mL) and stirred at room temperature for 3.5 h. The reaction mixture was filtered and the residue washed with hot ether. The ethereal solution was separated and dried ($MgSO_4$). Evaporation of the organic phase under vacuum to provide a crude product which was separated by preparative TLC (petroleum ether : ether : 7 : 10) to give 4-oxa-*exo*-epoxytricyclo[6.2.1.$0^{2,7}$]undeca-9-ene-3,6-diol **(5)** (0.08 g, 0.41 mmol) in 68.0% yield as a crystalline solid, m.p. = 128–129°C. IR (ν_{max}) (neat): 3310 (vs), 3025 (w), 2950 (s), 2880 (s), 1640 (w), 1040 (vs), 865 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.85 (2H, m), 4.5 (2H, d, J = 6 Hz), 3.2–3.8 (2H, m), 1.4–2.8 (8H, m) ppm. Anal. calcd. for $C_{11}H_{14}O_3$: C = 68.04; H = 7.21. Found: C = 68.15; H = 7.30.

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REFERENCES

1. M. Balci, Y. Sutbeyas and H. Secen, *Tetrahedron*, **46**, 3715 (1990).
2. (a) M. Balci, *Pure. Appl. Chem.*, **69**, 97 (1997); (b) A. Ptti, C. Sanfilippo, M. Piattelli and G. Nicolosi, *Tetrahedron: Asymmetry* **7**, 2665 (1996); (c) W.-W. Lee and S. Chang, *Tetrahedron: Asymmetry*, **10**, 2665 (1999).
3. M. Cere, G. Mantovani, F. Peri, S. Pollicino and A. Ricci, *Tetrahedron*, **56**, 1225 (2000).
4. W.-W. Lee and S. Chang, *Tetrahedron: Asymmetry*, **10**, 4473 (1999).
5. L. Ackermann, D-E. Tom and A. Furstner, *Tetrahedron*, **56**, 2195 (2000).
6. Y.U. Kwon and S.K. Chung, *Org. Lett.*, **3**, 3013 (2001).
7. (a) M. Mamaghani, *Tetrahedron*, **58**, 147 (2002); (b) M. Mamaghani and A. Alizadehnia, *J. Chem. Res.*, 386, (2002); (c) M. Mamaghani and A. Pourali, *Russ. J. Org. Chem.*, **38**, 347 (2002); (d) M. Mamaghani, A.J.H. Klunder and B. Zwanenburg, *J. Sci. I.R. Iran*, **11**, 205 (2000); (e) M. Mamaghani and A. Namazi, *J. Sci. I.R. Iran*, **10**, 169 (1999).
8. A.P. Marchand and R.W. Allen, *J. Org. Chem.*, **39**, 1596 (1974).
9. A.P. Marchand, W.D. Laroe, G.V.M. Shama, S.C. Suri and D.S. Reddy, *J. Org. Chem.*, **51**, 1662 (1986).
10. A. Ichihara, *Synthesis*, 207 (1987).

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