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Central core Uprolides a survey of some ring closing metathesis approaches

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ABSTRACT

The study of related to construction of central bicyclic core Uprolides D and E and the lactone fused to it mainly deals with the metathetic approaches. The 14-membered carbocyclic uprolides become excellent targets for RCM and ene-yne RCM with properly placing the diene and ene-yne systems.

Keywords: Uprolides D and E, Sodiumhydroxide, Trimethylsulfoxoniumiodide.

INTRODUCTION

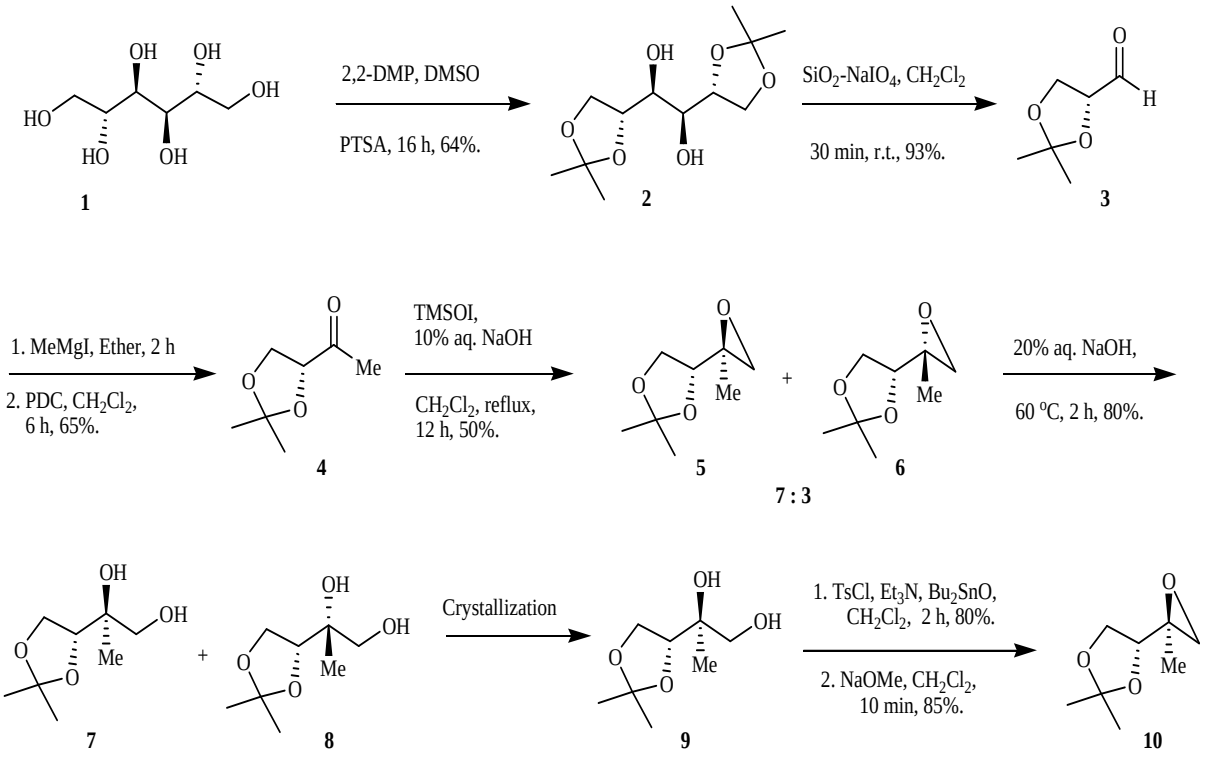
Terpenes are a large and varied class of hydrocarbons, produced primarily by a wide variety of plants, particularly conifers, and also by some insects such as swallowtail butterflies, which emit terpenes from their osmeterium. They are the major components of resin, and of turpentine produced from resin. The name "terpene" is derived from the word “turpentine”. Terpenes are derived biosynthetically from units of isoprene. The isoprene units may be linked together "head to tail" to form linear chains or they may be arranged to form rings. One can consider the isoprene unit as one of nature's preferred building blocks. Isoprene itself does not undergo the building process, but rather activated forms, isopentenyl pyrophosphate (IPP or also isopentenyl diphosphate) and dimethylallyl pyrophosphate (DMAPP or also dimethylallyl diphosphate), are the components in the biosynthetic pathway.

When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as terpenoids. Degradation products of terpenoids in which carbon atoms have been lost through chemical or biochemical processes may contain different numbers of carbon atoms, but their overall structure will indicate their terpenoid origin and they will be still considered as terpenoids. Terpenoids constitute the largest class of naturally occurring molecules from the plant kingdom and a major means of communication between plants and their environment. Terpenoids also play key roles in animal

development and physiology. Terpenoids are commercially important due to their use in a vast number of industrial products such as pharmaceuticals, flavoring agents, perfumes, insecticides, phytosanitary, coloring and anti-microbial agents. Some of the highly successful drugs from terpenoid family are Taxanes (cancer), Steroids (contraceptives, antiinflammatory), Artemisinin and derivatives (malaria).

Cembranolide compounds in general, have exhibited a range of unique modes of action. While none of these metabolites have demonstrated a sufficient level of activity or spectrum of activity to be commercialized, several have served as templates for the design of synthetic compounds. Uprolides D and E , the first representatives of a new family of furan integrated cembranolides, were recently isolated from the *Eunicea mammosa* collected at different locations around Puerto Rico.[3] As explained in the introduction novel macrocyclic skeleton and the relative configuration of were determined by extensive 2D NMR analyses. Biological testing of purified samples against different types of cancer cells revealed that these compounds have significant anticancer activity against HeLa cells, T-Cell leukemia, HCT 116 colon cancer, and MCF-7 breast adenocarcinoma. The combination of interesting anticancer activity and novel chemical structures makes the uprolides attractive targets for synthesis.

Scheme-1



MATERIALS AND METHODS

i. (1S, 2S)-1,2-Bis((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (2):

A mixture of powdered D-mannitol (60 g, 397 mmol), PTSA (0.31 g) and 2,2-dimethoxy propane (85.7 g, 823 mmol) in dry DMSO (100 mL) was stirred at rt. under anhydrous nitrogen. Within

one hour the suspended solid had dissolved and after 16 h the reaction mixture was poured into 3% aq. $NaHCO_3$ soln (300 mL). The mixture was extracted with ethyl acetate (4 X 500 mL) and the combined extracts inturn washed with water (1 x 500 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The solid residue obtained was recrystallized (2:8, ethylacetate:pet ether) to give diacetonide **2** (52 g, 60%) as colorless solid.

Mol. Formula	: $C_{12}H_{22}O_6$
^{1}H NMR($CDCl_3$, 500 MHz)	: δ1.35 (s, 6H), 1.41 (s, 6H), 2.62 (br s, 2H), 3.72 (d, *J* = 6.4 Hz, 2H), 3.96 (dd, *J* = 8.5, 5.6 Hz, 2H), 4.10 (dd, *J* = 8.5, 6.5 Hz, 2H), 4.16 (q, *J* = 6.4 Hz, 2H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	: δ 25.29 (q), 26.77 (q), 66.76 (t), 71.17 (d), 76.07 (d), 109.28 (s) ppm.
Elemental Analysis	Calcd.: C, 54.95; H, 8.45. Found: C, 54.88; H, 8.29.

ii. (R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (3):

To a vigorously stirred suspension of silicagel-supported $NaIO_4$ (76 g) in DCM (400 mL) was added a solution of diol **2** (10 g, 38 mmol) in DCM (100 mL). The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel and washed thoroughly with DCM (400 mL). The filtrate was concentrated to give aldehyde **3** (9.3 g, 93%) as colorless oil, which was directly taken for the next step without further purification.

Mol. Formula	: $C_6H_{10}O_3$
^{1}H NMR($CDCl_3$, 200 MHz)	: δ1.39 (s, 3H), 1.45 (s, 3H), 4.05-4.08 (m, 1H), 4.12-4.15 (m, 1H), 4.33-4.35 (m, 1H), 9.68 (d, *J* = 2.0 Hz, 1H) ppm.
^{13}C NMR($CDCl_3$, 50 MHz)	: δ25.11 (q), 26.22 (q), 65.49 (t), 79.76 (d), 111.14 (s), 201.53 (d) ppm.
Elemental Analysis	Calcd.: C, 55.37; H, 7.74. Found: C, 55.13; H, 7.55.

iii. (R)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanone (4):

To a solution of aldehyde **3** (15 g, 115 mmol) in dry ether (150 mL) was added freshly prepared solution of methyl magnesium iodide (230.5 mL, 1.0 M soln in ether, 230 mmol) slowly drop wise at 0 ^oC. The mixture was stirred for 2 h and the temperature was slowly raised to rt.. Excess Grignard was quenched with careful addition of sat. NH_4Cl at 0 ^oC. The reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The organic phase was separated and the aq. phase was in turn washed with ethyl acetate (2 X 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue obtained was dissolved in dry DCM (200 mL) and added flame dried 4A^o molecular sieves powder (20 g) and the reaction mixture was stirred at ice-cold temperature. Added PDC (86.5 g, 230 mmol) in portions at 0 ^oC followed by acetic anhydride (2 mL) and stirred at rt. for 6 h. DCM was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate (200 mL) and filtered through a pad of *celite*. The solid was washed with ethyl acetate (2 x 100 mL). The combined filtrates were concentrated and the residue was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give ketone **4** (10.8 g, 65%) as colorless oil.

Mol. Formula	: $C_7H_{12}O_3$
$[\alpha]_D$	+65.1 (*c* 1.5, benzene).
^{1}H NMR($CDCl_3$, 500 MHz)	δ 1.36 (s, 3H), 1.46 (s, 3H), 2.22 (s, 3H), 3.95 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.15 (t, *J* = 8.3 Hz, 1H), 4.35 (dd, *J* = 7.5, 5.6 Hz, 1H) ppm.

^{13}C NMR($CDCl_3$, 125 MHz)	δ 25.01 (q), 26.05 (q), 66.38 (t), 80.45 (d), 110.88 (s), 208.51 (s) ppm.
Elemental Analysis	Calcd. C, 58.32; H, 8.39. Found: C, 58.13; H, 8.25.

iv. (S)-2-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol (7):

To a solution of keto compound **4** (10 g, 69.36 mmol) in DCM (80 mL) was added trimethyl sulfoxonium iodide (15.26 g, 69.36 mmol) followed by a solution of 10% NaOH (27 mL). The reaction mixture was heated to reflux for 12 h and cooled. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The inseparable mixture of epoxides (**5**/**6**) were taken in 20% sodium hydroxide solution (60 mL) and heated to 60 ^oC for 2 h. Added aq. sat. NH_4Cl solution (100 mL) with ice cooling and the reaction mixture was extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (1:1 petroleum ether/ethyl acetate) followed by crystallization to give diol **7** (3.1 g, 25.4% overall) as colorless solid.

Mol. Formula	: $C_8H_{16}O_4$
M. P.	: 101 ^oC [lit 100-101 ^oC][13]
$[\alpha]_D$	: +6.2 (*c* 1.0, $CHCl_3$) [lit +5.14 (*c* 1.07, $CHCl_3$)][13]
IR ($CHCl_3$) $\tilde{\nu}$	: 3339, 1374, 1215 cm^{-1}.
^{1}H NMR($CDCl_3$, 500 MHz)	: δ1.16 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 2.22 (br s, 2H), 3.45 (d, *J* = 11.3, Hz, 1H), 3.61 (d, *J* = 11.3, Hz, 1H), 3.91 (t, *J* = 7.6 Hz, 1H), 4.01 (d, *J* = 7.6, Hz, 1H), 4.08 (d, *J* = 6.8 Hz, 1H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	: δ20.51 (q), 25.06 (q), 26.42 (q), 65.09 (t), 67.48 (t), 72.34 (s), 79.63 (d), 109.04 (s) ppm.
Elemental Analysis	Calcd.: C, 54.53; H, 9.15. Found: C, 54.35; H, 9.07.

v. (R)-2,2-Dimethyl-4-((R)-2-methyloxiran-2-yl)-1,3-dioxolane (10):

To a solution of diol **9** (2 g, 11.35 mmol) in dry DCM (20 mL) was added tosyl chloride (2.16 g, 11.35 mmol), dibutyl tin oxide (57 mg, 0.23 mmol) followed by triethylamine (3.2 mL, 22.7 mmol) and stirred at rt. for 2 h. DCM was removed under reduced and crude mixture was purified by column chromatography (7:3 petroleum ether/ethyl acetate) to give monotosylate (3 g, 80%) as colorless oil. To a solution of tosylate (3 g, 9.08 mmol) in dry DCM (20 mL) was added sodium methoxide solution (250 mg of Na in 4 mL of methanol, 10.89 mmol) with cooling and stirred for 10 min. added a sat. Solution of NH_4Cl (5 mL) and the mixture was diluted with DCM (10 mL). The organic phase was separated and the aq. phase inturn was washed with DCM (2 X 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to furnish epoxide **10** (1.22 g, 85%) as colorless oil.

Mol. Formula	: $C_8H_{14}O_3$
$[\alpha]_D$	: -2.07 (*c* 4.8, $CHCl_3$).
^{1}H NMR($CDCl_3$, 500 MHz)	: δ1.33 (s, 6H), 1.42 (s, 3H), 2.61 (d, *J* = 4.8 Hz, 1H), 2.71 (d, *J* = 4.8 Hz, 1H), 3.83 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.89 (t, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.8 Hz, 1H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	: δ16.73 (q), 25.01 (q), 26.14 (q), 52.29 (t), 56.14 (s), 65.75 (t), 77.81 (d), 109.72 (s) ppm.

Elemental Analysis Calcd.: C, 60.74; H, 8.92.
Found: C, 60.53; H, 8.95.

RESULTS AND DISCUSSION

Synthesis of -1,2-Bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (2):
The synthetic sequences started with D-mannitol (Scheme 2). D-mannitol was treated with 2,2-dimethoxy propane in dry DMSO by employing catalytic PTSA to afford 1,2:5,6-*bis*-O-isopropylidine-D-mannitol (**2**) in 84% yield.[11] Oxidative cleavage of **2** using silica gel impregnated sodium metaperiodate[12] gave the three-carbon synthon R-glyceraldehyde (**3**) in 93% yield. Subjecting **3** for methyl Grignard followed by PDC oxidation gave methyl ketone (**4**) in 65% overall yield (Scheme 2). The ^{1}H NMR spectrum and ^{13}C NMR were in full agreement with assigned structure. The keto-methyl resonated at δ 2.22 in ^{1}H NMR spectrum. Further ^{13}C NMR spectrum shown the keto carbonyl carbon and the methyl at δ 208.51 and 26.05 respectively. To transform the keto derivative **4** to the epoxide **10**, we opted for Corey-Chayvosky reaction which was studied under various reaction conditions to control the diastereoselectivity. The combination of trimethyl sulfonium iodide and NaH in dry DMSO gave regiomeric 7:3 inseparable mixture of epoxides (**10/6**) in 35% yield.[13] By little modification of the reaction condition (using trimethylsulfoxonium iodide in aq. sodium hydroxide as base) the yield can be improved up to 50% yield, however with similar diastereomeric selectivity.[14] The ratio was ascertained by ^{1}H NMR spectrum. The geminal epoxide protons of major isomer resonated at δ 2.61 and 2.70 as doublets (J = 4.8 Hz), where as for minor isomer, they were observed at δ 2.57 and 2.78 (J = 4.8 Hz). Since, these epoxides are inseparable, in order to procure pure epoxide, we intended to prepare the respective diols **9** and **8**, where one of them (**9**) was reported to be a solid and the other one as syrup.[13] Accordingly, treatment of the diastereomeric mixture of epoxides **10/6** with aq. sodium hydroxide provided the diols **9** and **8** mixture from which **9** could be separated by crystallization from a mixture of ethyl acetate-petroleum ether. The spectral as well as the analytical data of compound **9** was in agreement with the earlier reported data.

After having access to pure diol **9**, we next focused our attention of converting back diol **9** to the pure epoxide **10** and its opening with the dimethyl malonate. Regioselective tosylation[15] of **9** followed by treatment with sodium methoxide gave diasteromerically pure epoxide (**10**) in 85% yield. The NMR analysis and other analytical data were in full agreement with the assigned structure.

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