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Synthesis of dl-Pyroangolensolide

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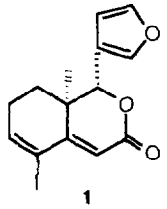
Abstract: A diastereoselective synthesis of dl-pyroangolensolide has been accomplished starting from 2,6-dimethylcyclohexenone in four steps in 62% yield. The key step involves an absolute threo selective aldol reaction.

Limonoids are secondary metabolites with a wide range of biological activities[1]. A common feature of several groups of the limonoid family is the unsaturated δ-lactone unit with a 3-furyl group substituent, a fragment found in pyroangolensolide **1**, which is obtained from the pyrolysis of methyl angolensate[2].



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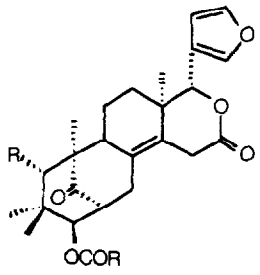
Examples of related bioactive compounds are the antifeedant **2**[3] and the antagonist of platelet activating factor **3**[4].



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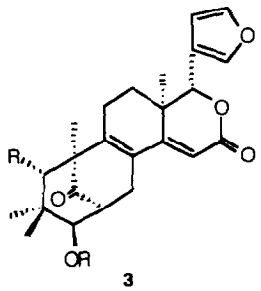

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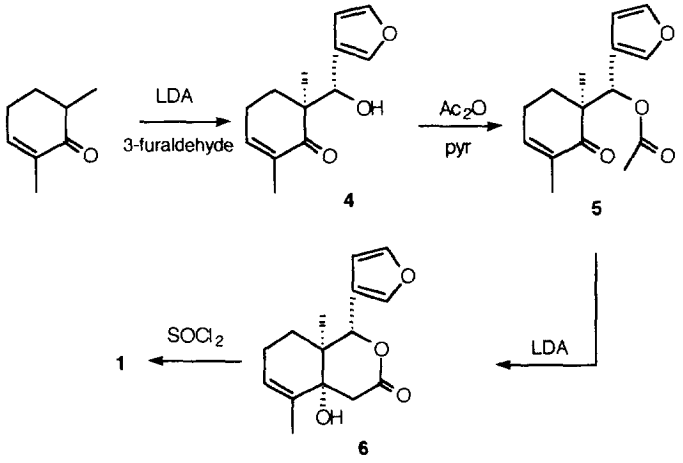
Despite their growing biological interest there are few approaches to the synthesis of this type of limonoids. In keeping with a search for simple synthetic methods applicable to limonoids such as **1-3** and related compounds, we undertook a stereochemical study of the aldolic reaction between aromatic aldehydes and cyclohexenone enolates. We have found that kinetic addition of 3-furaldehyde to 2,6-dimethylcyclohexenone in THF afforded exclusively the threo aldol isomer in good yield[5]. This highly stereoselective aldolic addition has been the key step in a short synthesis of pyroangolensolide **1**, which we described below.

Three syntheses of dl-pyroangolensolide have been reported by Grieco[6] (12%), Tokoroyama[7] (8%) and Fernández-Mateos[8] (44%). However, a mixture of isomers was obtained in all cases.

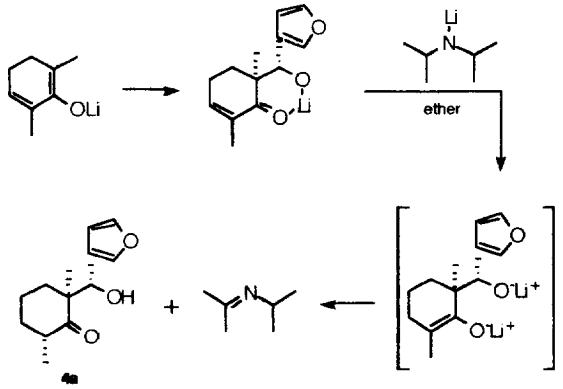
Our synthesis of dl-pyroangolensolide **1** was achieved in a four-step sequence from the readily available 2,6-dimethylcyclohexenone[9] (Scheme 1).



Scheme 1

Condensation of lithium enolate of the 2,6-dimethylcyclohexenone with 3-furaldehyde in THF at -78°C afforded the threo aldol **4** in 81% yield. If the aldolic condensation is carried out in ether instead of THF, a mixture of two aldols is obtained in the 3:1 ratio in 83% yield. The major addition product is the aldol **4** and the minor product has been identified as **4a**[8].

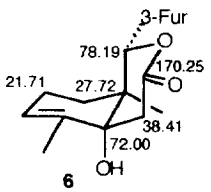
The formation of this aldol **4a** could be explained by hydride transference from LDA to the enone system after aldolic addition[10] (Scheme 2).



Scheme 2

The aldol **4** was acetylated quantitatively with acetic anhydride in a mixture of pyridine and methylene chloride to give the keto acetate **5**.

Intramolecular aldol reaction of the unsaturated keto acetate **5** was promoted by lithium diisopropylamide in THF at -78°C to give only the hydroxy lactone **6** in 81% yield. The structure proposed for the hydroxy lactone **6** was supported by ^{1}H and ^{13}C NMR spectra and by the structure of the dehydration product. The stereochemical outcome of the cyclization can be rationalized by considering steric factors[11]. In agreement with this argument, the cis byciclic lactone **6** would be expected. The ^{1}H and ^{13}C data of this lactone **6** (mp 154-156°C) are very similar to those exhibited by the saturated analog **7**[8].



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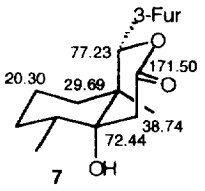

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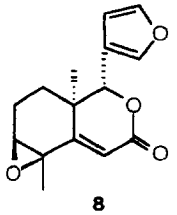
Dehydration of the hydroxy lactone **6** with thionyl chloride in pyridine-methylene chloride at 0°C for 5 min afforded the racemic pyroangolensolide **1** (mp 145-146 °C) in 95% yield.

Epoxidation of pyroangolensolide **1** by several procedures (H_2O_2, NaOH; mCPBA, CH_2Cl_2; dimethydioxirane) results in the monoepoxide **8**[12], an isomer of the known naturally occurring calodendrolide **9**[13].



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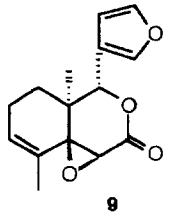

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Experimental.

General Methods. Melting points were determined on a hot-stage apparatus and are not corrected. The ^1H and ^{13}C spectra were recorded in $CDCl_3$ solution at 200 MHz for proton. IR spectra were obtained as thin films. Reactions requiring anhydrous conditions were performed in flame-dried glassware under a positive pressure of dry N_2. Flash column chromatographies were carried out using silica gel 60 (0.040-0.063 mm Merck). Organic extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. All crystalline product were recrystallized from hexane-ether.

6-(3-Furylhydroxymethyl)-2,6-dimethyl-2-cyclohexenone 4.- (In THF) A solution of n-BuLi (2.7 ml, 4.32 mmol) in hexane (1.6 M) was added dropwise at 0°C with stirring under N_2 to a solution of diisopropylamine (0.61 ml, 4.4 mmol) in THF (11 ml). The resulting mixture was stirred at 0°C for an additional 15 min. The mixture was then cooled at -78°C, and the 2,6-dimethylcyclohexenone (500 mg, 4 mmol) was added dropwise. Stirring was continued at -78°C for 25 min; then 3-furaldehyde (0.35 ml, 4 mmol) was rapidly added. After 20 min a saturated aqueous NH_4Cl was added and the resulting heterogeneous mixture was stirred and gradualy warmed to room temperature (45 min). The organic layer was separated and the aqueous phase was extracted twice with ether. The combined extracts were washed with water and brine and then dried (Na_2SO_4). Evaporation of the solvent left crude product mixtures which were separated by flash chromatography (hexane-ether: 90-10) to yield the aldol **4** (718 mg, 81 %): IR ν_{max} (film) 3450, 3000-2900, 1654, 1642, 1023, 874 cm^{-1}; NMR ^1H ($CDCl_3$) δ: 1.12 (3H, s), 1.73 (3H, br s), 2.24 (2H, m), 4.84 (1H, s), 6.31 (1H, m, H-β'), 6.67 (1H, br s), 7.29 (1H, m, H-α'), 7.30 (1H, m, H-α) ppm; NMR ^{13}C ($CDCl_3$) δ: 14.94, 15.69, 22.16, 30.46, 47.34, 71.01, 109.87, 124.13, 133.54, 140.14, 141.94, 145.10, 200.05 ppm. Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.85; H, 7.36.

(In ether) By the same procedure used above 2,6-dimethylcyclohexenone (174 mg, 1.4 mmol) in ether (3.5 ml) afforded the aldol **4** (197 mg, 63%) and the saturated aldol **4a** (63 mg, 20%): m.p. 117-118 °C; IR ν_{max} (film) 3460, 3000-2846, 1694,1596 cm^{-1}; NMR ^1H ($CDCl_3$).δ: 0.97 (3H, s), 1.05 (3H, d, J=6.5 Hz), 2.78 (1H, m), 5.24 (1H, s), 6.37 (1H, m, H-β'), 7.38 (1H, m, H-α'), 7.39 (1H, m, H-α) ppm; NMR ^{13}C ($CDCl_3$) δ: 15.12, 16.99, 20.36, 35.80, 36.98, 41.42, 53.12, 70.03, 109.72, 124.82, 140.12, 142.73, 218.00 ppm.

Acetylation of 6-(3-Furylhydroxymethyl)-2,6-dimethyl-2-cyclohexenone 4.- The aldol **4** (220 mg, 1 mmol) was treated with acetic anhydride (1.2 ml) and pyridine (1.2 ml) at room temperature for 4 h. The reaction mixture was poured into ice, and the heterogeneous mixture was stirred and gradually warmed to room temperature (1 h). It was then extracted three times with ether. The extracts were washed with aqueous HCl (2 N), $NaHCO_3$ (5 %) and brine and then dried (Na_2SO_4). The solvent was evaporated to afforded the keto acetate **5** (260 mg, 100 %): IR ν_{max} (film) 3000-2830, 1742, 1720, 1660 cm^{-1}; NMR ^1H ($CDCl_3$) δ: 1.16 (3H, s), 1.73 (3H, m), 2.05 (3H, s), 2.31 (2H, m), 6.30 (1H, m, H-β'), 6.35 (1H, s), 6.62 (1H, m), 7.31 (1H, m, H-α'), 7.32 (1H, m, H-α) ppm. Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.91. Found: C, 68.71; H, 6.94.

1-(3-Furyl)-4a-hydroxy-5,8a-dimethyl-3,4,4a,7,8,8a-hexahydro-1H-2-benzo-pyran-3-one 6.- A solution of keto acetate **5** (250 mg, 0.96 mmol) in dry THF (2 ml) was added dropwise at -78

°C with stirring under N_2 to a solution of lithium diisopropylamide (1.05 mmol) in THF (2.6 ml), prepared as shown in preceding reaction. The mixture was stirred at -78 °C for 3 h, and then saturated aqueous NH_4Cl was added and the mixture was stirred and gradually warmed to room temperature. After the usual workup the solvent was evaporated and the residue was purified by flash chromatograpy (hexane-ether: 60-40) to afforded the hydroxylactone **6** (203 mg, 81 %): mp 154-156 °C; IR ν_{max} (film) 3440, 3000-2850, 1723 cm^{-1}; NMR ^1H ($CDCl_3$) δ: 1.01 (3H, s), 1.86 (3H, m), 2.81 (1H, d, J=19 Hz), 3.03 (1H, d, J=19 Hz), 5.29 (1H, s), 5.69 (1H, m), 6.44 (1H, m, H-β'), 7.42 (1H, m, H-α'), 7.44 (1H, m, H-α) ppm; NMR ^{13}C ($CDCl_3$) δ: 15.44, 18.58, 21.71, 27.72, 38.41, 40.36, 72.01, 78.19, 109.78, 121.33, 126.06, 135.32, 140.58, 142.97, 170.25 ppm. Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.91. Found: C, 68.70; H, 6.89.

dl-Pyroangolensolide 1.- $SOCl_2$ (0.11 ml, 1.4 mmol) was added at 0 °C with stirring under N_2 to a solution of the hydroxylactone **6** (180 mg, 0.68 mmol) in dry CH_2Cl_2 (3.4 ml) and dry pyridine (0.22 ml, 2.7 mmol). The mixture was stirred at 0 °C for 5 min and then poured into ice. The mixture was gradually warmed to room temperature, it was then extracted three times with CH_2Cl_2. The combined extracts were washed with aqueous HCl (2N), $NaHCO_3$ (5 %), and brine and then dried (Na_2SO_4). The solvent was evaporated, and pyroangolensolide **1** (160 mg, 95 %) was obtained: mp 145-146 °C (lit.[14] mp. 145.0-145.5 °C); IR ν_{max} (film) 3160, 3000-2850, 1713, 1630, 1597, 1260, 880 cm^{-1}; NMR ^1H ($CDCl_3$) δ: 1.02 (3H, s), 1.88 (3H, m), 2.26 (2H, m), 5.12 (1H, s), 5.83 (1H, s), 6.13 (1H, m), 6.44 (1H, m, H-β'), 7.42 (1H, m, H-α'), 7.48 (1H, m, H-α) ppm; NMR ^{13}C ($CDCl_3$) δ: 15.84, 18.73, 22.02, 29.88, 37.15, 80.62, 109.93, 109.93, 120.15, 129.15, 136.03, 140.99, 142.69, 159.77, 165.74 ppm.

Epoxidation of Pyroangolensolide 1.- **Method A.-** A solution of m-chloroperoxibenzoic acid (50 mg, 0.25 mmol) in dry CH_2Cl_2 (0.5 ml) was added dropwise at room temperature a solution of pyroangolensolide **1** (20 mg, 0.08 mmol) in dry CH_2Cl_2 (0.5 ml) and the resulting mixture was stirred at this temperature for an additional 22 h. A solution of $NaHSO_3$ (10 %) was added, and the resulting heterogeneus mixture was stirred for 15 min. The mixture was extracted with ether and the extracts were washed with a solution of NaOH (0.5 N), water, and brine and then dried (Na_2SO_4). Evaporation of the solvent gave 1-(3-furyl)-5α,6α-epoxy-5β,8a-dimethyl-3,5,6,7,8,8a-hexahydro-1H-2-benzopyran-3-one **8** (17 mg, 80 %): mp 171-173 °C; IR ν_{max} (film) 2924, 1709, 1273 cm^{-1}; NMR ^1H ($CDCl_3$) δ: 1.01 (3H, s), 1.54 (3H, s), 3.27 (1H, s), 5.10 (1H, s), 6.28 (1H, s), 6.40 (1H, m, H-β'), 7.41 (1H, m, H-α), 7.45 (1H, m, H-α') ppm; NMR ^{13}C ($CDCl_3$) δ: 17.10, 20.00, 23.59, 23.59, 36.40, 60.10, 66.00, 80.80, 109.90, 118.43, 120.00, 141.28, 143.10, 162.19, 164.30 ppm. Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 69.25; H, 6.21.

Method B.- To a stirred solution of pyroangolensolide **1** (50 mg, 0.20 mmol) in methanol (1.8 ml) maintained under N_2 at 0 °C was added H_2O_2 (0.32 ml, 40 %). To this solution was added NaOH (0.1 ml, 6N, 0.58 mmol). The solution was stirred for 70 h at room temperature and then poured into a solution of $NaHCO_3$ (10 %) The aqueous solution was extracted with ether, dried (Na_2SO_4), filtered and concentrated to afford the epoxide **8** (43 mg, 82 %).

Method C.- To a solution of pyroangolensolide **1** (20 mg, 0.08 mmol) in CH_2Cl_2 (0.7 ml) at room temperature was added freshly distilled dimethyldioxirane solution (1.3 ml, 0.13 mmol,) in acetone (0.1M)

and the resulting mixture was allowed to stand at 20 °C for 72 h. The solvent was removed under reduced pressure to yield a residue (24 mg) which was chromatographed on silica gel. Elution with hexane-ether (80-20) afforded epoxide **8** (12 mg, 84 %).

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References and Notes.

1 Champagne, D.E.; Koul, O.; Isman, M.B.; Scudder, G.G.; Towers, G.H.N. *Phytochemistry* **1992**, 377.

2. Davis, J.B.; Godfrey, V.M.; Jewers, A.H.; Manchada, A.H.; Robinson, F.V.; Taylor, D.A.H. *Chemistry and Industry* **1970**, 201. Ibid **1972**, 976.
3. Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. *J. Chem. Soc. Perkin Trans I* **1993**, 995.
4. Kadota, S.; Yanagawa, K.; Kikuchi, T.; Tanaka, K. *Tetrahedron Lett.* **1990**, 5943.
5. Fernández-Mateos, A.; Pascual Coca, G.; Pérez Alonso, J.; Rubio González, R.; Tapia Hernández, C. *Tetrahedron Lett.* **1995**, 961.
6. Drewers, S.E.; Grieco, P.A.; Huffman, J.C. *J. Org. Chem.* **1985**, *50*, 1309.
7. Tokoroyama, T.; Ketsuji, Y.; Fukuyama, Y. *J. Chem. Soc. Perkin Trans I* **1988**, 445.
8. Fernández Mateos, A.; de la Fuente Blanco, J.A. *J. Org. Chem.* **1991**, *56*, 7089.
9. Kende, A.S.; Fludzinski, P.; Hill, J.H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *108*, 3551.
10. The reduction of aldehydes to alcohols by hydride transference from LDA has been reported by: Majewski, M. *Tetrahedron Lett.* **1988**, 4057.
11. Spencer, T.A.; Neel, H.S.; Ward, D.C.; Williamson, K.L. *J. Org. Chem.* **1966**, *32*, 434.
12. The proposed β orientation of oxiranic oxygen in epoxide **8** is based on the easier approach of the peracid from the opposite face to angular methyl group. The same stereochemistry for a similar reaction has been reported by Tokoroyama, T.; Ketsuji, Y.; Matsuyama, H.; Shimura, T.; Yokotani, K.; Fukuyama, Y. *J. Chem. Soc. Perkin Trans I* **1990**, 1745.
13. Cassady, J.M.; Liu, Ch. *J. Chem. Soc. Chem. Comm.* **1972**, 86.
14. Fukuyama, Y.; Tokoroyama, T.; Kubota, T. *Tetrahedron Lett.* **1973**, 4869.

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