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Stereoselective Access to Polyfunctionalized Decalins

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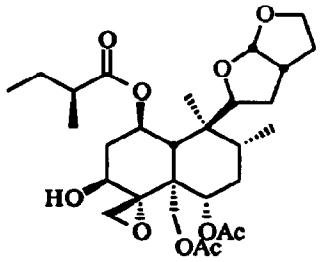
Abstract: As a model of a stereoselective approach to ajugareptansin **1**, a versatile and straightforward access to polyfunctionalized *cis* or *trans* decalins is presented. It is based on a Lewis acid-mediated addition of furan to the unsaturated ketoester **3** followed by oxidative opening of the furan to give *cis* decalins by an aldolisation process. Selective epimerization at carbons 5 or 10 is described and allows the access to the *trans* ring geometry.

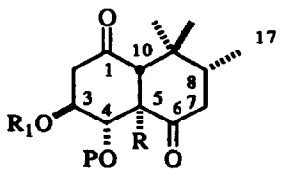
Highly polyfunctionalized decalin systems are present in many biological active natural products. Our interest in the antifeedant activities of ajugareptansin **1** [2] led us to investigate new approaches aimed towards the construction of the decalinic moiety of this molecule.

In continuation with our previous work on condensation of furans[3] with activated cyclohexenone in the presence of $BF_3.Et_2O$ as catalyst, we report here the results of our efforts to control the relative configurations at carbons 3, 4, 5, 8, and 10 [4] in a model compound **2** bearing a methyl group at carbon C-8.



1

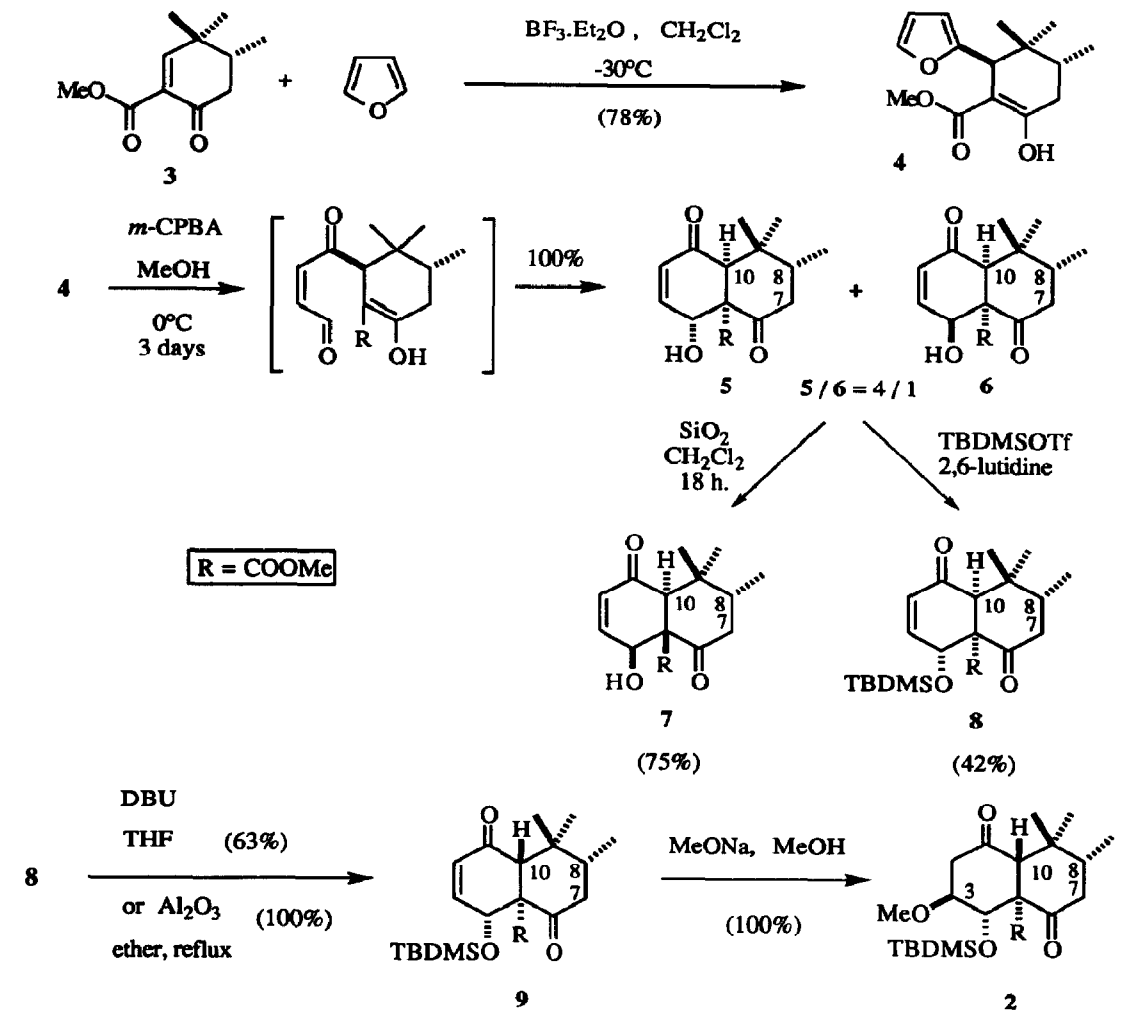
Ajugareptansin



R = COOMe
P = protective group
R_1 = Me

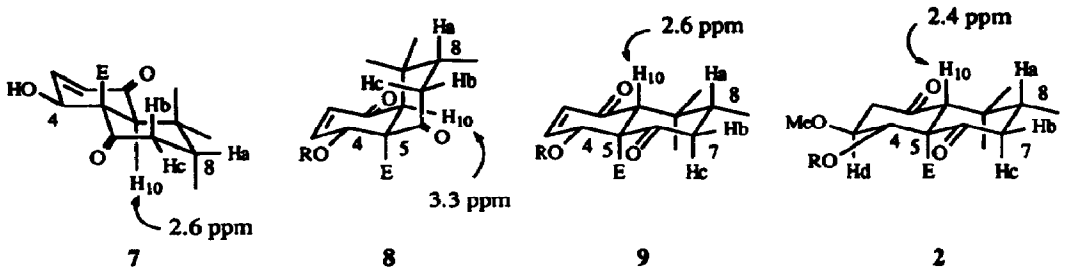
2

The Lewis acid-mediated addition of furan on the ketoester **3** [5] was found to be fully controled with respect to the methyl group at C-8, leading to **4** [6] in 78% yield as a single diastereomer. Oxidative ring opening of the furan system using *m*-chloroperoxybenzoic acid (*m*-CPBA) in anhydrous methanol led to a mixture of the two diastereomeric *cis* decalins **5** and **6** [7] in high yield in a 4/1 ratio. We assume that this reaction proceeds through an unsatured 1,4-dicarbonyl intermediate[8] *via* an intramolecular aldolisation process.[3]



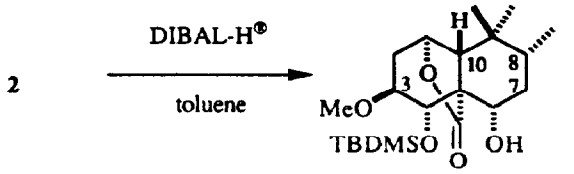
Attempts to purify this mixture by flash chromatography on silica gel gave, in addition to compounds **5** and **6**, a new product to which the structure **7** [9] was assigned as explained below. We had previously demonstrated in a similar case[3] that silica gel was able to promote a retroaldolisation / aldolisation process yielding the thermodynamically more stable *trans* system.[10] When the OH group at C-4 position was protected as a TBDMS ether[11] prior to chromatography, the *cis* decalin **8** [12] was isolated in 42% overall yield. Epimerization at C-10 of the protected compound was obtained either by using DBU in anhydrous THF (63%) or quantitatively with alumina in refluxing diethyl ether.[13] Introduction of an oxygen atom at C-3 was achieved by sodium methoxide, leading to **2** [15] in quantitative yield.

The structure assignments for compounds **7**, **8**, **9**, and **2** were supported by extensive NMR experiments and the X-ray crystallography[16] of compound **10** obtained quantitatively by DIBAL-H® reduction of compound **2**.

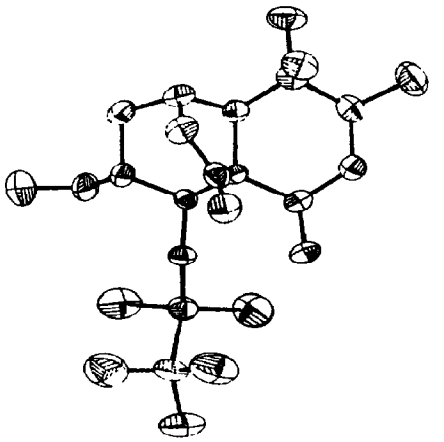


7 8 9 2

R = TBDMS E = COOMe



2 10



OR ΓEP drawing of **10** (enantiomer)

For the *trans* ring junction (**7**, **9** and **2**), H-10 resonates at 2.6, 2.6 and 2.4 ppm. For the *cis* junction (**5**, **6** and **8**), this resonance is shifted to lower field (3.6, 3.2 and 3.3 ppm) due to the anisotropy of the close methyl ester at C-5. A high value of the coupling constant between H_a and H_c in **9** (J = 13.5 Hz) and **2** (J = 14 Hz) is in agreement with the proton H_a in axial position in both structures. In **7**, H_a displays two smaller coupling constants (4 and 6 Hz), proving that H_a is in equatorial position.

The strategy developed here allows for a versatile and stereocontrolled access to either of the four highly functionalized decalins **7**, **8**, **9** and **2** from the easily prepared intermediate **4**. These results in hand, we now have good hope to reach the *trans* decalinic moiety of ajugareptansin.

References and Notes

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   Poirel, C., *Bull. Mens. ONC*, **1993**, *180*, 18-23.
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4. Refered to the numbering of clerodans.
5. Unsaturated ketoester **3** was prepared from 4,4-dimethylcyclohex-2-enone using the following sequence : 1) Me_2CuMgI, ether, 0°C (94%) ; 2) NaH, $CO(OMe)_2$, refluxing DME (70%) ; 3) PhSeCl, pyridine, 0°C then H_2O_2,(82%).
6. All the new compounds were fully characterized by NMR, IR and MS.
7. Compound **5** : ^1H NMR (400 MHz, $CDCl_3$, ppm) : 2 - 2.1 (m, 1H, H-8), 2.4 (dd, 1H, J = 5 and 15 Hz, H-7b), 3 (dd, 1H, J = 4.8 and 15 Hz, H-7c), 3.6 (s, 1H, H-10).
   Compound **6**: ^1H NMR (400 MHz, $CDCl_3$, ppm) : 2 - 2.1 (m, 1H, H-8), 2.3 (dd, 1H, J = 4 and 16 Hz, H-7b), 2.6 (dd, 1H, J = 12 and 16 Hz, H-7c), 3.2 (s, 1H, H-10).
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   Williams, P. D.; Le Goff, E., *J. Org. Chem.*, **1981**, *46*, 4143-4147.
9. Compound **7** : ^1H NMR (400 MHz, $CDCl_3$, ppm) : 2 (m, 1H, H-8), 2.18 (dd, 1H, J = 4 and 15 Hz, H-7b), 2.6 (s, 1H, H-10), 3.03 (dd, 1H, J = 6 and 15 Hz, H-7c).
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12. Compound **8**: ^1H NMR (400 MHz, $CDCl_3$, ppm) : 2.1 - 2.2 (m, 1H, H-8), 2.3 (dd, 1H, J = 15 and 8.5 Hz, H-7b), 2.7 (dd, 1H, J = 15 and 5.5 Hz, H-7c), 3.3 (s, 1H, H-10) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) : 56.2 (C-10), 67.3 (C-4), 129.8 (C-2), 169.3 (C-11), 197. (C-1), 206 (C-6).
13. Mukhopadhyav, A.; Ali, S. M.; Usain, M.; Suriawanshi, S. N.; Bhakuni, D. J., *Tetrahedron Lett..*,**1989**, *30*, 1853-6.
14. Compound **9** : ^1H NMR (400 MHz, $CDCl_3$, ppm) : 1.6 - 1.7 (m, 1H, H-8), 2.3 (dd, 1H, J = 13.5 and 3.5 Hz, H-7b), 2.6 (s, 1H, H-10), 2.8 (t, 1H, J = 13.5 Hz, H-7c), 5.2 (t, 1H, J = 2 Hz, H-4), 6 (dd, 1H, J = 2 and 10.3 Hz, H-2), 6.3 (dd, 1H, J = 2.3 and 10.3 Hz, H-3) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) : 60.6 (C-10), 69.4 (C-4), 130 (C-2), 144.5 (C-3), 195 (C-1), 204 (C-6).
15. Compound **2**: ^1H NMR (400 MHz, $CDCl_3$, ppm) : 2.1 - 2.3 (m, 2H, H-2a and H-7b), 2.4 (s, 1H, H-10), 2.8 (t, 1H, J = 13.5 Hz, H-7c), 3 (dd, 1H, J = 5.5 and 14 Hz, H-2a), 3.5 - 3.6 (m, 1H, H-3), 4.5 (d, 1H, J = 7 Hz, H-4) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) : 52.2 and 56.3 (2 OCH_3), 61.4 (C-10), 72.7 (C-4), 81 (C-3), 172 (C-ester), 202.8 and 203.6 (C-1 and C-6).
16. We gratefully thank Pr. T. Prangé for X Ray crystallographic analyses.

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