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EFFICIENT METHOD FOR THE PREPARATION OF 2α,3β-DICHLORO-4,4,10-TRIMETHYLDECALIN SYSTEMS AS A ROUTE FOR THE SYNTHESIS OF DICHLOROLISSOCLIMIDE

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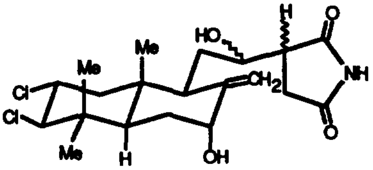
Summary: An efficient synthesis of diequatorial dichlorinated trimethyldecalin derivatives, analogues of the AB ring of the strongly cytotoxic agent dichlorolissoclimide 1, is described. The key step involves a thermal diaxial to diequatorial dichloride rearrangement in good yield.

Dichlorolissoclimide 1 is a labdane diterpene which has not only extremely potent cytotoxic activity [IC_{50} 1 μg/ml (P_{388}); 14 μg/ml (human KB)] but also a very unusual structure, containing a vicinal trans-diequatorial dichloride and a succinimide unit.[3] The unusual diequatorial dichloride is a synthetic challenge since addition of chlorine to a cyclohexene - even an extremely hindered one such as a $\Delta^{9,11}$ steroidal olefin - gives mainly the trans-diaxial dichloride[4] and there are no other routes for the preparation of diequatorial dichlorides of this sort in the literature. We describe herein a preparation of this novel substructure by a simple and efficient diaxial to diequatorial rearrangement of a properly substituted dichloro terpenoid, a process that should be applicable for the synthesis of dichlorolissoclimide 1 and its analogues.



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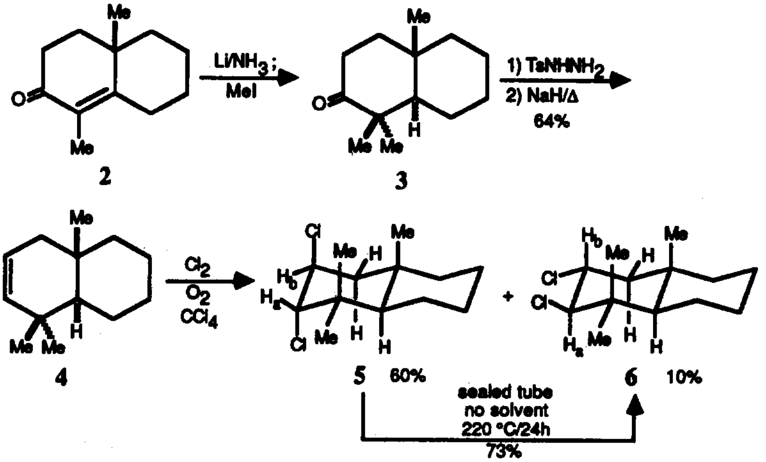
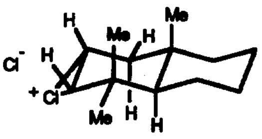
The kinetic product of chlorination of a 4,4,8a-trimethyloctahydronaphthalene such as 4 would be mainly the trans-diaxial dichloride 5. However, we anticipated that this compound could be isomerized into the more stable trans-diequatorial dichloride 6 upon heating. MM2 calculations estimate the energy difference between the two products to be 2.8 kcal/mol in favor of the diequatorial isomer 6. The rearrangement of diaxial to diequatorial dihalides[5] works well for many steroid systems, including 2,3- and 5,6-dibromo,[5ab] 2,3-chlorobromo[5b] and even 2,3-chloroacetoxy[5c] compounds. Although no dichloro rearrangements have been described in the literature,[6] we believed that they could be effected although higher temperatures might be necessary, since the leaving group ability of chloride is much lower than that of bromide. The alkene we chose to test this chlorination-rearrangement process, 4,4,10-trimethyloctalin **4**, was synthesized as follows. Reductive methylation of the known dimethyloctalone **2**[7] afforded the trimethyldecalone **3** in excellent yield.[8] Shapiro-Bond reaction of **3** (namely, formation of the tosylhydrazone and elimination with sodium hydride) furnished the trimethyloctalin **4**. Chlorination of this alkene produced a 6:1 mixture of diaxial and diequatorial dichlorides in which the diaxial **5** greatly predominated over the diequatorial isomer **6**. However, when the diaxial compound **5** was heated neat in a sealed tube at 220 °C for 24h, the diequatorial dichloride **6** was isolated in 73% yield. The structures of these compounds are easily assigned from their ^{1}H NMR spectra, in which the low field protons show distinctive coupling patterns: for **5**: H$_a$ d, $J = 4$ Hz; H$_b$ pseudoquartet (actually a ddd), $J \cong 4$ Hz; for **6**: H$_a$ d, $J = 10.6$ Hz; H$_b$ d of t, $J \cong 10.6$, 4 Hz, as expected. The mechanism of this rearrangement presumably involves the formation of the chloronium chloride **7** (or, less likely, its stereoisomer) from **5** by ejection of the 2β chlorine atom by the 3α one.[9] This intermediate can then be opened to regenerate the diaxial dichloride **5** or produce the more stable diequatorial dichloride **6**. After several hours, mainly the diequatorial product is observed.[10] Thus the overall yield of the diequatorial dichloride **6** from **4** is greater than 50%.





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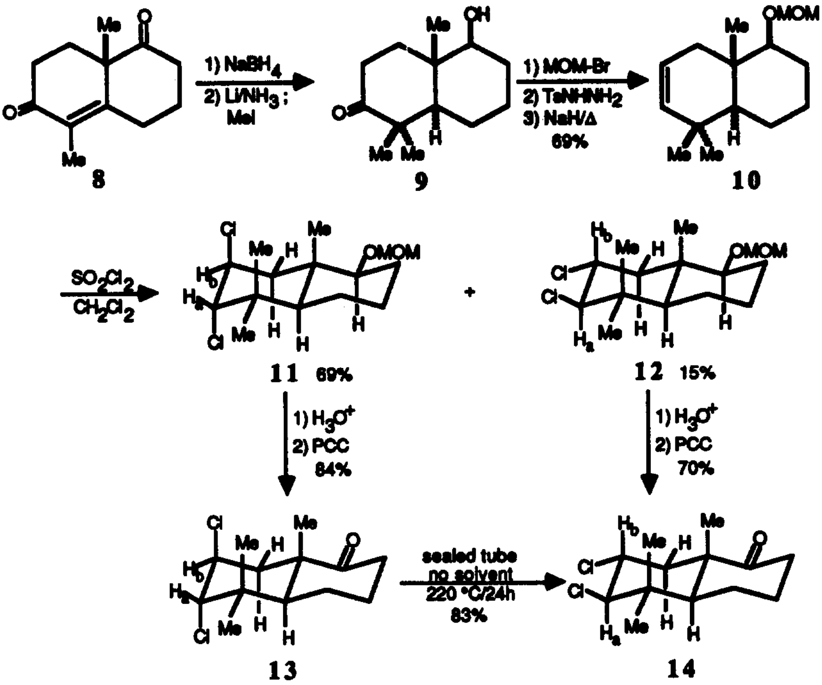
Other functionality survives these rearrangement conditions. For example, we have successfully carried out the rearrangement of the ketone **13**, which was prepared as follows. Reduction of the ketone **8** and reductive methylation



of the resulting hydroxyenone afforded the known ketoalcohol 9.[11] Protection of the alcohol as the MOM ether and Shapiro-Bond reaction furnished the alkene 10 in 69% overall yield. Chlorination of 10 afforded an approximately 4.5:1 mixture of the two expected products, 11 and 12, with the diaxial dichloride 11 being the major isomer. Acidic hydrolysis of the MOM ether of 11 and PCC oxidation of the resultant alcohol furnished the ketone 13. The same sequence afforded the isomeric product 14 from the isomeric dichloro MOM ether 12.[12] As before, when compound 13 was heated without solvent at 220 °C for 24h, the diequatorial dichloride 14 was formed in 83% yield.[13] Thus carbonyl functionality is well tolerated in this thermal process and the diequatorial dichloro ketone 14 is available from the alkene 10 in 60% overall yield. However, the corresponding dichloro MOM ether 11 gave a mixture of several products upon attempted rearrangement at high temperatures, thus implying that ethers do not survive the thermal conditions for rearrangement.

Thus we have developed a new route to diequatorial dichlorides of the type found in the important antitumor agent dichlorolissoclimide 1 via a thermal rearrangement of the kinetically favored diaxial dichlorides. We are currently attempting to use this sequence on other derivatives related to 1 and to convert the dichloroketone 14 into dichlorolissoclimide 1 and its analogues.

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References and Notes

1) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.

2) Recipient of the Ramon Areces Foundation Fellowship, 1992-4.

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6) There is one report of a diaxial to diequatorial dichloride rearrangement in a steroid case [Giese, H. J.; Romers, C. *Acta Cryst.* **1966**, *20*, 257]. They reported that heating 2β,3α-dichlorocholestane at 200° C for 1-2 h produced the 2α,3β-isomer but no yields or details were given.

7) Hansson, L.; Carlson, R.; Sjöberg, A.-L. *Acta Chem. Scand.* **1990**, *44*, 1036.

8) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

9) One can also postulate a dipolar transition state in which the chlorine atom move concertedly across the top and bottom faces on the molecule to arrive at the isomeric dichloride. For a discussion of similar dibromo steroid cases, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*, Wiley Interscience: New York, 1965, pp. 294-5.

10) A small amount (approximately 3-4%) of the diaxial dichloride **5** is recovered from the reaction. This is in good agreement with the MM2 energy difference between **5** and **6** (2.8 kcal/mol) which would predict a 5.5 : 94.5 equilibrium ratio at 220 °C (493 K), assuming no significant entropy difference between the two isomers.

11) Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663.

12) Compounds **13** and **14** also showed the same pattern of coupling constants seen for the isomeric dichlorides **5** and **6**, with **13** exhibiting small couplings for both H_a (d) and H_b (q) and **14** showing a single large coupling for H_a with H_b being a large triplet of small doublets, as expected. Similar coupling patterns were also seen for compounds **11** and **12**.

13) A small amount (approximately 3%) of the diaxial dichloride **13** is recovered from the reaction. Here the MM2 calculations predict an energy difference of 2.4 kcal/mol, which would translate into an equilibrium of 92 : 8.

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