A Stereochemically Controlled Intramolecular Diels–Alder Approach to the Octahydronaphthalene Fragment of Dihydromevinolin

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An enantiospecific route to the octahydronaphthalene (**22**) from L-glutamic acid is described: the key step is the intramolecular Diels–Alder reaction (**19**) to (**22**).

In recent years a series of fungal metabolites, the mevinic acids (**1**)—(**4**), have been isolated[1] and shown to inhibit 3-HMG-CoA reductase, a key enzyme in cholesterol biosynthesis.[2] Their ability to lower blood cholesterol levels in patients suffering from hypercholesterolemia have made these compounds important synthetic targets. The majority of the work[3] has concentrated on the synthesis of compactin (**4**) and dihydrocompactin (**3**), whereas mevinolin (**2**) and dihydromevinolin (**1**), with a methyl substituent at C-6, appear to be the more active compounds.[1]

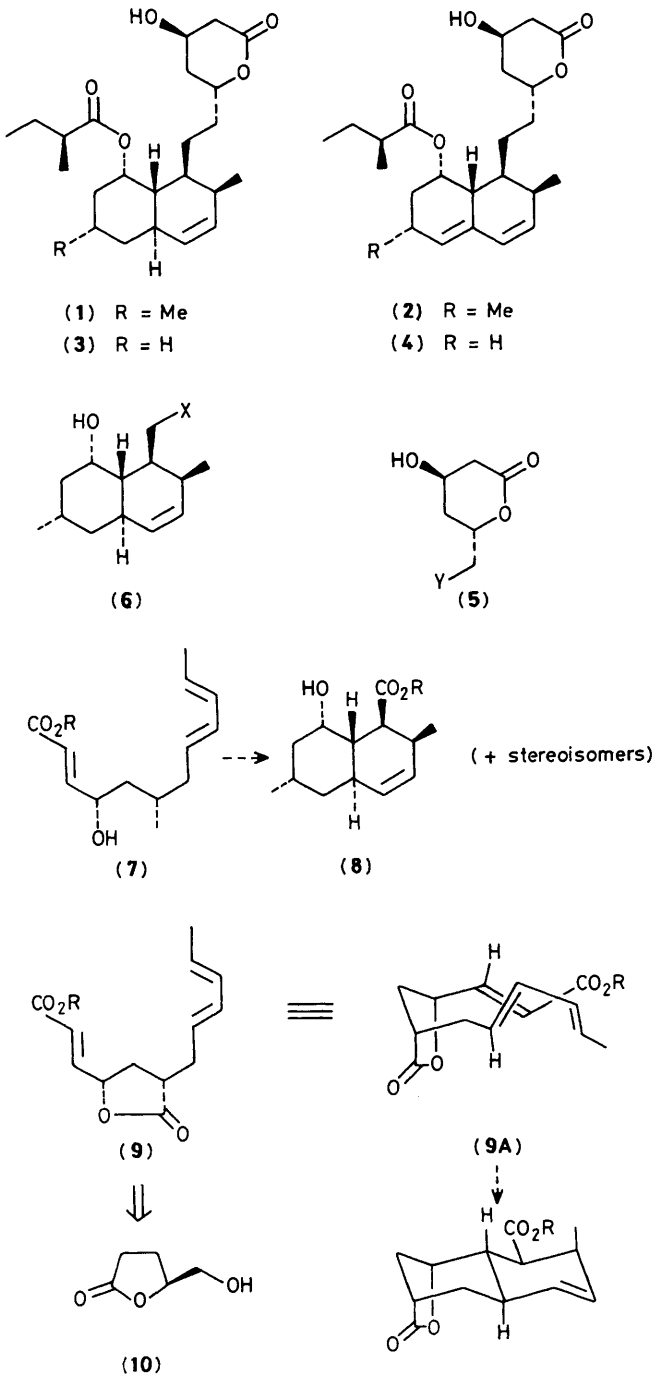
It has been shown in the dihydrocompactin (**3**) series that bromination of the 3,4-double bond followed by dehydrobromination gives the diene system required for compactin.[4] Dihydromevinolin (**1**) was therefore chosen as the synthetic target owing to its higher activity and the possibility that mevinolin (**2**) could be prepared using a similar route.

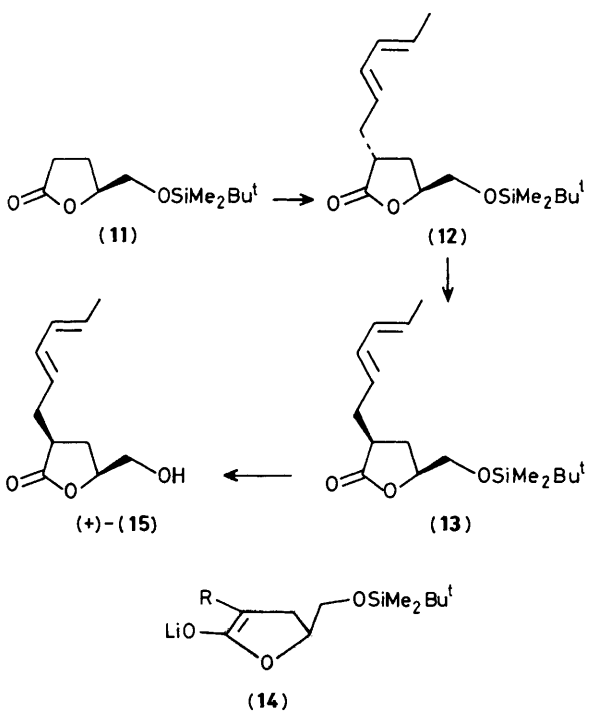
Dihydromevinolin was disconnected into two fragments, the δ-lactone (**5**) and the octahydronaphthalene (**6**). The major problem to overcome in the synthesis of (**6**) was the control of stereochemistry at the six chiral centres. One obvious route[4,5] involved the intramolecular Diels–Alder reaction (**7**) to (**8**), but three other stereoisomers could be formed, and it was difficult to predict the effect that the two chiral centres in the bridging chain would have on the stereochemical course of the reaction.[6] Hence a method was required to control this reaction such that only the desired isomer was produced. A further problem was the synthesis of the triene with the correct relative and absolute stereochemistry.

It appeared that a possible method of controlling the Diels–Alder reaction was to link the two chiral centres *via* a five-membered lactone ring (**9**). By reducing the flexibility of the triene it was hoped to alter the energies of the reacting conformations such that the one (**9A**) leading to the desired isomer should be the most favoured. This approach would also simplify the synthesis since the stereochemistry would have to be controlled about a ring rather than in an open chain. A further advantage was that the starting lactone (**10**) could be obtained in optically pure form from L-glutamic acid permitting the synthesis of (**9**) with the correct absolute stereochemistry.

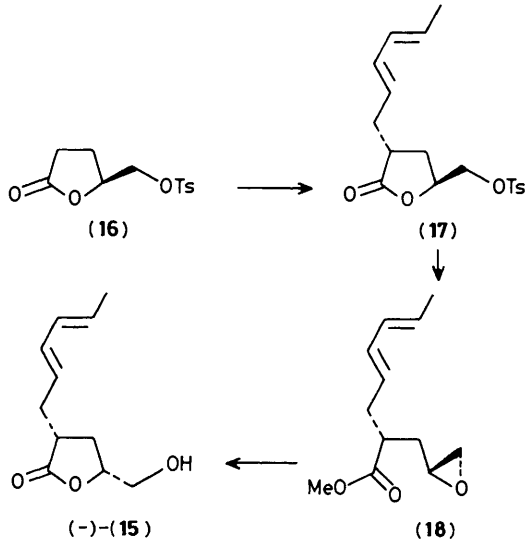
The lactone[7] (+)-(**10**) was converted into the silyl ether (**11**) and alkylated with 1-bromohexa-2,4-diene. When this reaction was quenched at −78 °C a 14 : 1 ratio of *trans* : *cis* isomers was obtained but when the mixture was allowed to warm to room temperature and quenched after 8 h a 3 : 2 *trans* : *cis* ratio was obtained.[8] The two isomers could be easily separated by flash column chromatography and the combined yield was 75%. It was hoped that the *trans*-isomer (**12**) could be epimerised into the *cis*-isomer (**13**) by protonation of the enolate (**14**) from the least hindered face.[9] Despite using various proton sources the best ratio that could be obtained was 2 : 3 *trans* : *cis*. The yield, however, was extremely high and recycling of the *trans*-isomer gave, after deprotection, the *cis*-alcohol (+)-(**15**) in 60% overall yield from (**10**) (Scheme 1).

An alternative approach to the alcohol (**15**) was developed. This involved epimerisation at C-4 rather than C-2 (Scheme 2).[10] For dihydromevinolin the (−)-enantiomer of the lactone (**10**) is required which is available from the more expensive D-glutamic acid, and the sequence was therefore developed using the readily available (+)-enantiomer of (**10**) as a model.





Scheme 1



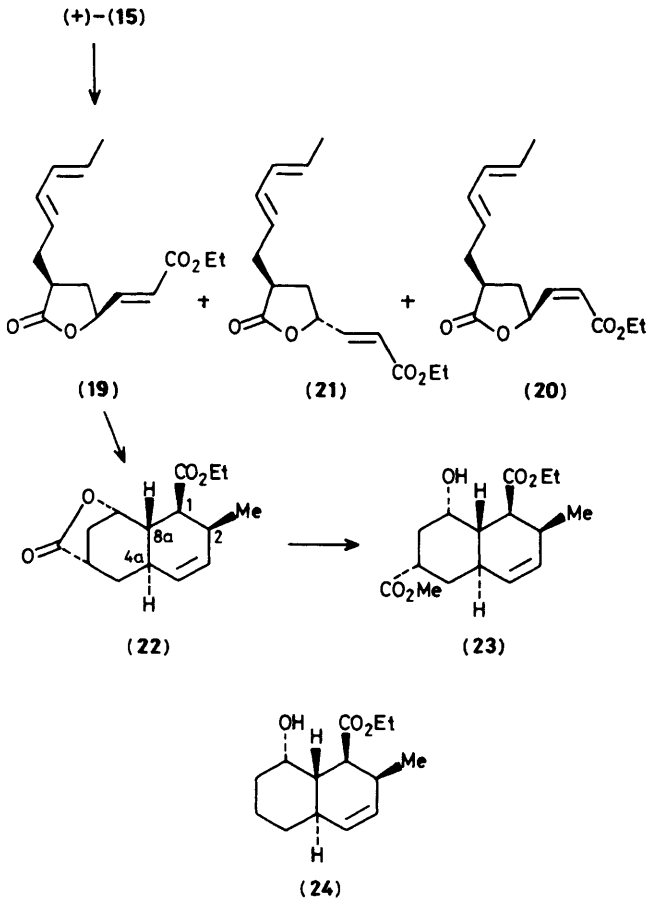
Scheme 2. Tos = p-$MeC_6H_4SO_2$.

Conversion into the toluene-*p*-sulphonate (**16**) and alkylation with 1-bromohexa-2,4-diene gave the *trans*-isomer (**17**). Opening of the lactone ring with MeOH–K_2CO_3 gave the ester–epoxide (**18**). This was ring closed (CF_3CO_2H, C_6H_6) with inversion of stereochemistry at C-4 to give the (−)-enantiomer of the *cis*-alcohol (**15**). The optical rotations of the alcohols (+)-(**15**) and (−)-(**15**) were +35.2 and −35.8° respectively.

Oxidation of the alcohol (+)-(**15**) proved troublesome owing to the difficulty of isolating the resultant aldehyde and the ease with which this material epimerised at C-4. This problem was overcome by carrying out a Swern oxidation and trapping the aldehyde *in situ* with the stabilised Wittig reagent.† This procedure gave the desired triene (**19**) in 75% overall yield from (**15**) together with 5% of (**20**) and 10% of (**21**). The triene was heated in a sealed tube at 140 °C for 120 h in xylene and gave a single isomer in 75% isolated yield.‡ The stereochemistry of the lactone (**22**) obtained was deduced

† A similar procedure has recently been reported: R. E. Ireland, D. Häbich, and D. W. Norbeck, *J. Am. Chem. Soc.*, 1985, **107**, 3271; R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.

‡ The reaction can also be carried out by heating the triene at 210 °C for 24 h but under these conditions a small amount (~8%) of another isomer is formed.



from the 360 MHz ^{1}H n.m.r. data. The proton H-8a (δ 1.75, t, *J* 12 Hz) is diaxially coupled to H-4a (δ 2.35, br.t, *J* 12 Hz) and H-1 (δ 2.88, dd, *J* 12 and 6 Hz). This would indicate that H-8a, H-4a, and H-1 are all axial and H-2 equatorial. Opening of the lactone ring with LiOMe gave the ester–alcohol (**23**) whose n.m.r. spectrum was very similar to that reported[4] for the compactin precursor (**24**) [(**23**), data for (**24**) in parentheses: H-8, δ 4.28 (4.28) br.s; H-1, δ 2.9 (2.88), dd, *J* 11.5 (12.2), 6 (6) Hz].

In conclusion we have developed a six-step synthesis, overall yield 30%, of lactone (**22**), which has the correct absolute stereochemistry at all six chiral centres for the octahydronaphthalene fragment of dihydromevinolin.

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