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Stereoselectivity in Natural Product Synthesis

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In the modern era of chemical synthesis the difference between relative and absolute configuration was understated. The main thing was to prove the constitution and relative configuration of a synthetic target compound. A racemic mixture at the end of a synthesis was tolerated in most cases. If really necessary, a resolution would help.

The post-modern era of chemical synthesis began with two epochal events. 1963 was the year of the epistemologically famous Patchouli Alcohol Case[1]. In 1971 a Robinson annelation with exceedingly high enantioselectivity was reported[2]. Life of the synthesizing chemist was considerably changed by these two events: it was eased by the former and became more interesting by the latter. Turning away from the dogma that synthesis above all had to serve structure determination, relieved restraint of using only those reactions the products of which would be safely predictable. Aiming at enantiomerically pure target compounds opened the chemist's eyes to look at the whole problem of stereoselection.

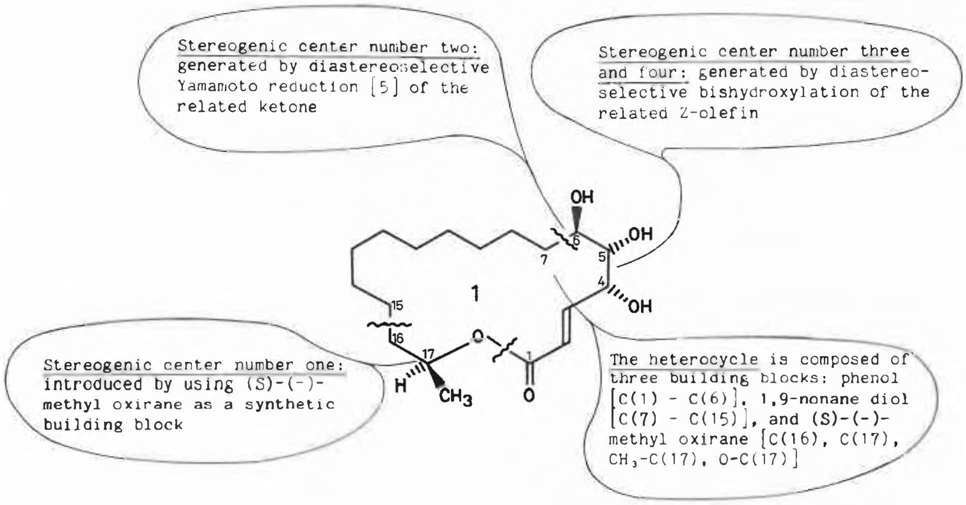
There is no general progress possible in synthetic methodology without particular progress in the synthesis of enantiomerically pure target compounds. Directional change occurs by shift of emphasis on specific elements of a reacting system. Emphasis is going to change from the cultivation of optically active substrates to the cultivation of optically active reagents and from there to the cultivation of optically active catalysts.

Long-Range Conformational Transmission of Chiral Information in Large Ring-Sized Lactones

(+)-Aspicillin (**1**) is build up from phenol, 1,9-nonanediol, and (*S*)-(−)-methyloxirane (cf. Fig. 1)[3]. The latter building block supplies the first stereogenic center, C-17. The lactone ring is produced by photolactonization[4], as early as possible during the course of the synthesis. The central question of the whole synthesis is, whether in 18-membered ring lactones long-range conformational transmission of chiral information from a stereogenic center (C-17) to a remote molecular site (C-6), where another stereogenic center is going to be generated, is possible in a predictable way. Yamamoto reduction[5] generates *R*-configuration at C-6 with an extremely high diastereoselection in the required direction (96% yield of a mixture of the (6*R*)- and (6*S*)-epimers in a ratio of 99.6:0.4).

The first two equivalents of the organoaluminium compound form a complex with the substrate (the IR-band of both carbonyl groups are shifted by 80 units to lower wavenumbers). As the conformation of the resulting supermolecule is not known, the direction of diastereoselection is not predictable.

L-Selectride[6] generates the *S*-configuration at C-6 with strikingly high diastereoselection, albeit not in the synthetically desired direction (82% yield of a mixture of the (6*R*)- and (6*S*)-epimers in a ratio of 3:97). To explain this result, a conformational change preceeding borohydride reduction is necessary.


Stereogenic center number two: generated by diastereoselective Yamamoto reduction [5] of the related ketone

Stereogenic center number three and four: generated by diastereo-selective bishydroxylation of the related Z-olefin

Stereogenic center number one: introduced by using (S)-(-)-methyl oxirane as a synthetic building block

The heterocycle is composed of three building blocks: phenol [C(1) - C(6)], 1,9-nonane diol [C(7) - C(15)], and (S)-(-)-methyl oxirane [C(16), C(17), CH_3-C(17), O-C(17)]

*Fig. 1. Outline of the strategic concept for the synthesis of (+)-aspicilin (***1***)*[3]*: construction of the heterocycle (by photolactonization*[4]*) and generation of the four stereogenic centers.*

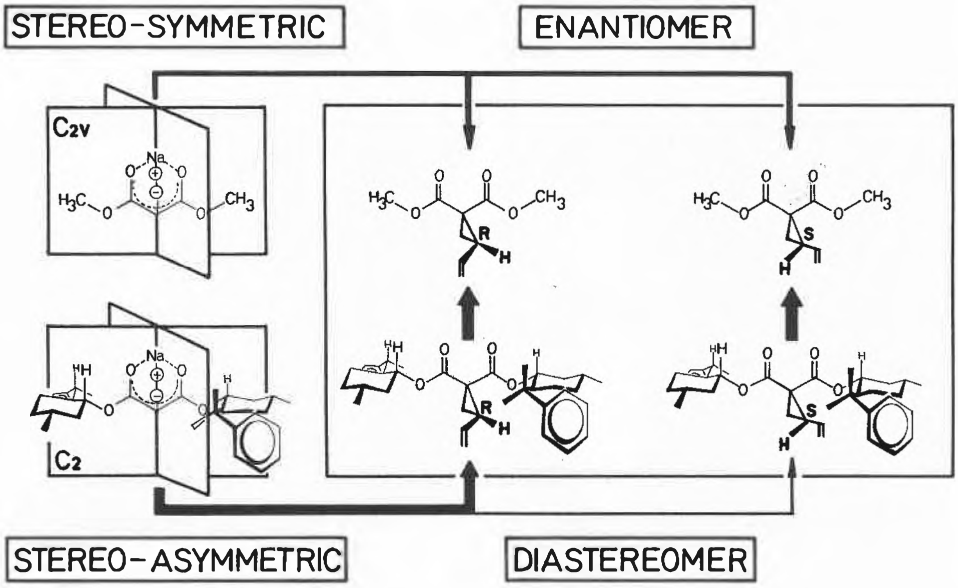


Fig. 2. Stereo-symmetric Linstead cyclopropanation[8] *of the C_{2v}-symmetric chelate (top part) affording a racemic mixture of the dimethyl 2-vinylcyclopropane-1,1-dicarboxylates. Stereo-asymmetric Linstead cyclopropanation*[9] *of the C_2-symmetric chelate (bottom part) furnishing predominantly the R-diastereomer of di[8-phenylmenthyl] 2-vinylcyclopropane-1,1-dicarboxylate.*

From C_2-Symmetric Malonates to Three-Membered Ring Building Blocks with Predictable Sense of Chirality

According to *Linstead*[7], a sequence of inter- and intramolecular alkylations driven tandem, using (*E*)-1,4-dibromo-2-butene, converts an appropriate malonate into the related 2-alkenyl-substituted cyclopropane-1,1-dicarboxylate. The achiral chelate, in which the enolate anion of dimethyl malonate is attached to the sodium cation, in a stereo-symmetric Linstead cyclopropanation affords a mixture of the enantiomeric dimethyl 2-vinylcyclopropane-1,1-dicarboxylates in a ratio of 1:1 (cf. Fig. 2, top part).

If, however, the chiral, non-racemic chelate in which the enolate anion of di[8-phenylmenthyl] malonate is attached to the sodium cation, a stereo-asymmetric Linstead cyclopropanation furnishes a mixture of the diastereomeric di[8-phenylmenthyl] 2-vinylcyclopropane-1,1-dicarboxylates in a ratio of 98:2 (cf. Fig. 2, bottom part). The *R*-configuration of the major product component has been predicted by conformational analysis of the product-determining transition structure[10] and shown to be correct by X-ray structure analysis[11].

Since (+)-8-phenylneomenthol[11] and (−)-8-phenylmenthol[12] behave almost like enantiomers, stereo-asymmetric Linstead cyclopropanation of the C_2-symmetric chelate, in which the enolate anion of di[8-phenylneomenthyl] malonate is attached to the sodium cation, gives a mixture of the diastereomeric di[8-phenylneomenthyl] 2-vinylcyclopropane-1,1-dicarboxylates in a ratio of 8:92, in favour of the *S*-diastereomer[13]. In each case the major product component has been isolated and, after transesterification converted into (*R*)- or (*S*)-dimethyl 2-vinylcyclopropane-1,1-dicarboxylate, respectively. The three-membered ring building blocks have been expanded stereospecifically into the related 2-alkyl-3-alkenyl-substituted cyclopentanones[9, 13] (cf. Fig. 3).

Enantioselective Conjugate Addition of Optically Active Reagents Made of an Organocuprate Complexed with a Chiral Ligand

According to Fig. 3 compound **2** is accessible more directly from 2-methyl-2-cyclopentenone. Enantioselective conjugate addition of the relevant organocuprate complexed with (*S*)-(−)-2-(methoxymethyl)pyrrolidine[14] affords in 76% yield a mixture of **2** and *ent*-**2** in a ratio of 88:12[15]. *Corey* et al.[16] have recently reported results of an initial investigation of enantioselective conjugate addition of alkyl groups to 2-cyclopentenone.

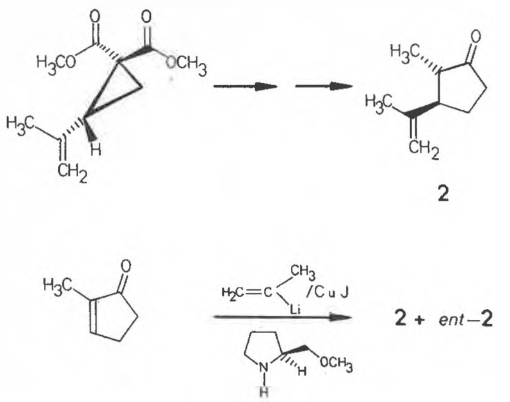


Fig. 3. Formation of the five-membered ring building block **2** *by stereospecific ring expansion*[13] *of (R)-(+)-dimethyl 2-isopropenylcyclopropane-1,1-dicarboxylate or by enantioselective conjugate addition (together with ent-***2***) to 2-methyl-2-cyclopentenone*[15].

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