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ABSOLUTE AND RELATIVE CONFIGURATION OF L-660,631

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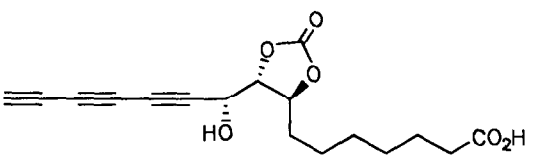
Summary: The relative and absolute stereochemistry of the potent antifungal agent L-660,631 has been determined to be **1** by synthesis of an appropriate degradation product.

Triynecarbonate L-660,631 (**1**), isolated from *actinomycetes* fermentation broths, is a new broad spectrum antifungal agent active *in vitro* against pathogenic yeasts and filamentous fungi.[1] This compound is a potent pre-squalene inhibitor of sterol biosynthesis in *Candida albicans*.[2] Elucidation of the gross structure of this compound has been reported previously.[1] Triynecarbonate **1** is highly unstable and must be handled only in dilute solutions, as neat preparations polymerize rapidly, often violently, under ambient conditions. Due to its rather intractable nature, and the difficulty in preparing suitable crystalline derivatives for crystallographic analysis, a synthetic chemical study was undertaken in order to determine the absolute and relative stereochemical configuration of this molecule.

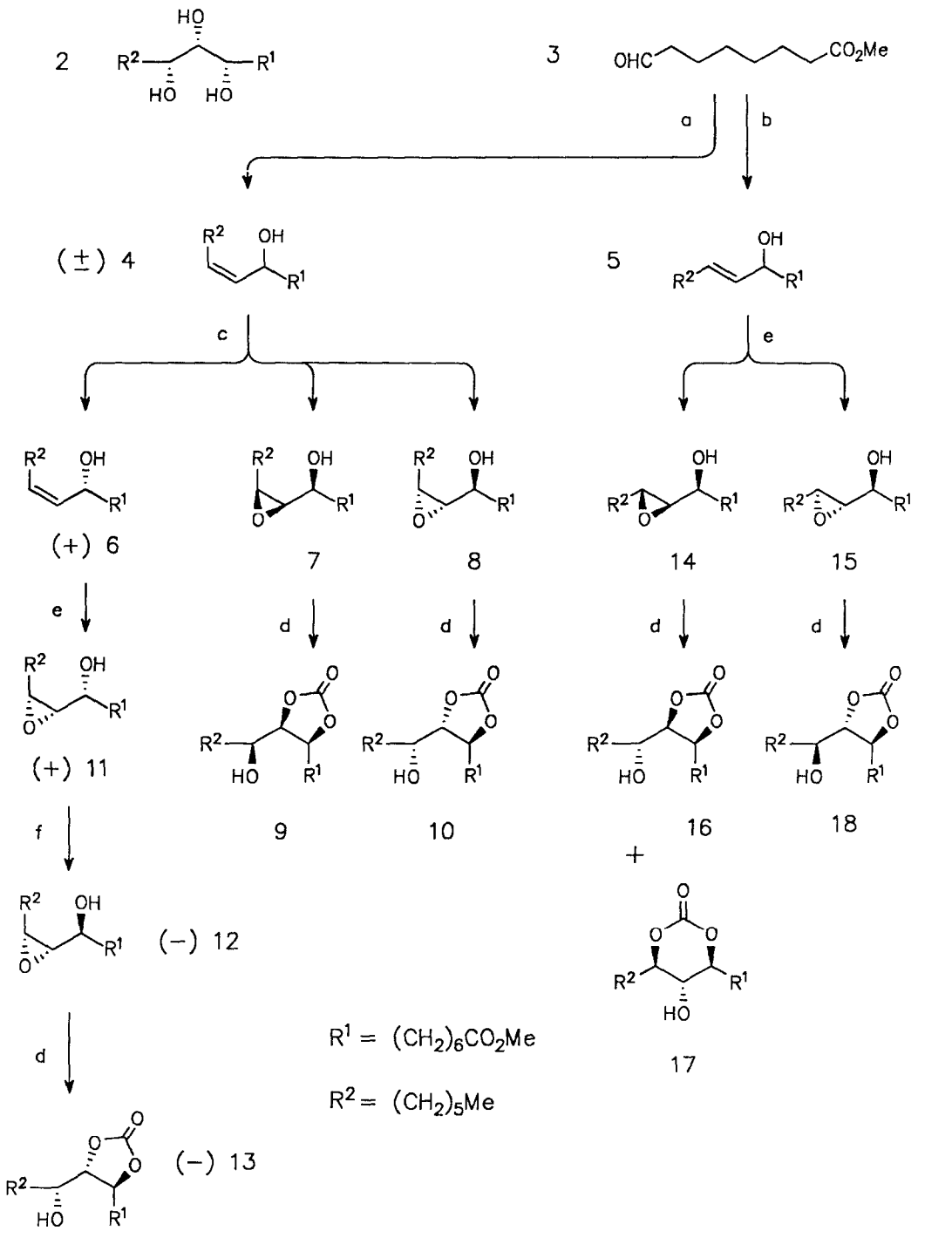
1 L-660,631



In order to complete the determination of the relative and absolute stereochemistry of L-660,631 (**1**), it was necessary to synthesize the chemically stable perhydro methyl ester **13**.[3,4] Tentative assignment of the relative stereochemistry to be that of configuration **10** had been made based on reaction and NMR data of the triol derivative **2**.[4,5] The perhydro carbonate isomer of this configuration was synthesized first, along with the isomer having configuration **9**, from the *cis* olefin **4**. When **10** proved to be the correct relative stereochemistry, the absolute stereochemistry was determined by synthesis of the same isomer in optically active form. Then, to complete the proof, the other two isomers of configuration **16** and **18** were synthesized from the *trans* olefin **5** in order to confirm that all such isomers could be distinguished from one another by 300 MHz NMR.

Necessary for the elaboration to the desired target compounds were quantities of both *cis* and *trans* allylic alcohols **4** and **5**. Treatment of lithium octyne with 7-formyl methylheptanoate[6] followed by Lindlar reduction[7] afforded the *cis* allylic alcohol **4** in adequate yield.[4] Reaction of the DIBAL-methyl lithium derived ate complex[8] of 1-octyne with the same aldehyde yielded the *trans* allylic alcohol **5** in an expedient fashion.[4]

Formation of the *erythro* epoxide **8** from the *cis* olefin under non-stereospecific conditions proved difficult. Using the Sharpless conditions[9] without added chiral tartrate ligand produced only the *threo* form **7**, which lead to a carbonate of



Reaction conditions: a)i. $LiC{\equiv}C(CH_2)_5Me$, THF, -78°, 52%; ii. H_2, Pd/Pb-$CaCO_3$, hexanes, 99%. b) reagent from [i. 1-ocytne, neat DIBAL, 50°; ii. MeLi, RT], heptane, -78°, 23%. c) $Ti(OiPr)_4$, L-(+)-diethyl tartrate, *t*BuOOH, 3Å sieves, CH_2Cl_2, 0°, 10% **6**, 66% **7**, 23% **8**. d)i. PhNCO, Py, RT, 54-93%; ii. $BF_3{\cdot}OEt_2$, Et_2O, -20°, 65-72%. e) 100% MCPBA, CH_2Cl_2, 80-92%. f)i. PDC, HOAc, CH_2Cl_2, 3Å sieves, 78%; ii. $Zn(BH_4)_2$, Et_2O, 76%.

configuration **9**, not to the carbonate of the predicted configuration **10**. However, epoxidation *with* a chiral ligand present produced a mixture of both *threo* and *erythro* epoxides in a 3:1 ratio, making it the key step in the synthesis of both the racemic and chiral epoxides. The enantiospecific Sharpless epoxidation was thus used to kinetically resolve the racemic mixture of olefin **4**.[9] When L-(+)-diethyl tartrate[10] was utilized as the chiral ligand, the remaining starting material **6** retained optical activity of a predictable configuration (93-94% optical purity at 90% completion, as determined by use of the chiral shift reagent $Eu(hfbc)_3$ and 400 MHz NMR).[4,11] The epoxidation products, *threo* **7** and *erythro* **8** epoxides of unknown enantiomeric excess[4], were then used in the synthesis of carbonates **9** and **10** in order to determine the relative stereochemistry. Because only a 10% yield of optically enhanced **6** had been obtained from the kinetic resolution of racemic **4**, epoxidation of both enantiomers of **4** must have occurred. This renders these epoxides, **7** and **8**, useless for the purpose of elucidating the absolute configuration of **13**. The kinetic resolution was run close to complete conversion in order to ensure that a sufficiently high enough enantiomeric excess was obtained such that ORD measurement comparisons would be rendered unambiguous. In order to establish the relative configurations of the two *cis*-olefin derived epoxy-alcohols **7** and **8**, a sample of the more polar **7** was oxidized by PDC[13] and then reduced with zinc borohydride[14] to form the *erythro* epoxy-alcohol. That this corresponded to the less polar epoxy-alcohol **8** establishes the relative configurations of the two compounds in question.

Formation of the carbonates **9** and **10** from the ∝-epoxy-alcohols **7** and **8** proved straightforward as shown.[15] Epoxide opening and carbonate formation proceeded cleanly at -23°C, each urethane forming a *single* carbonate, clearly distinct from each other by 300 MHz NMR.[4] As predicted, the NMR of carbonate **10**, derived from the *erythro* epoxide, corresponded exactly to the 300 MHz NMR of the naturally derived perhydro carbonate, confirming that the relative stereochemistry is indeed as depicted for **1**.

Formation of the optically active carbonate **13** did not prove as straightforward. No method could be found to convert the optically active *cis* olefin **6** directly to the *erythro* epoxide. Instead the optically active olefin was epoxidized by MCPBA to produce mostly the optically active *threo* epoxide **11** (*threo*:*erythro* 14:1).[4] Next, the *threo* epoxide was oxidized by PDC[13] to the ∝-epoxy-ketone[4] and stereospecifically reduced by zinc borohydride[14] to the *erythro* epoxide **12**.[4,16] As a check on the stereospecificity of the oxidation and reduction steps, the rotation of the *erythro* epoxy-alcohol **12** produced in this manner was compared with the rotation of the trace of *erythro* epoxy-alcohol formed directly from epoxidation by MCPBA. As predicted, the ORD measurements were opposite in sign and of the same value within the error of the measurement.[17]

The formation of the optically active carbonate **13** from the *erythro* epoxy-alcohol was performed in the same manner as for the racemic epoxy-alcohols.[4,15] Both the ORD and the sign of the CD measurements of the rotation of the synthetically produced carbonate **13** were in agreement with the same data obtained from the naturally derived carbonate **13**, proving that the absolute stereochemistry of L-660,631 is as shown in **1**.[18]

As final proof of the stereochemistry of L-660,631, the other two diastereomers of configurations **16** and **18**, were synthesized from the *trans* olefin **5**. As expected, epoxidation of the *trans* olefin with MCPBA was not stereospecific as it had been for the *cis*, the *erythro* and *threo* epoxy-alcohols **14** and **15** being formed in a 1:1 ratio.[4] The diastereomeric identity of **14** and **15** was established by oxidation of the more polar **14** with PDC[13] and subsequent reduction with zinc borohydride[14] to afford **15** in a manner similar to that used to confirm the identity of the *threo* and *erythro* *cis*-olefin derived epoxy-alcohols **7** and **8**. Formation of carbonate **18** from epoxy-alcohol **15** was carried out in an identical manner as for the *cis* derived epoxy-alcohols. However, during the opening of epoxy-alcohol **14**, along with the desired carbonate **16**, was isolated the *endo* opening product **17**, as might be expected from stereochemical considerations.[4,19] Each carbonate was clearly distinct from the other three, including the naturally derived form **13**, by 300 MHz NMR.

References and Notes:

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2. Onishi, J. C.; Abruzzo, G. K.; Fromtling, R. A.; Garrity, G. M.; Milligan, J. A.; Pelak, B. A.; Rozdilsky, W. *Ibid.*
3. This compound was available in 81% yield from natural L-660,631 *via* catalytic reduction with 10% Pd-C in methanol, followed by *brief* treatment with ethereal diazomethane.
4. Satisfactory spectral data was obtained for this compound.
5. This compound was available from reduction with LAH in THF of naturally derived **13** in moderate yields. When compound **2** was treated with 2,2-dimethoxypropane and TSA in acetone followed by acetylation in pyridine, only two *very* similar (by 300 MHz NMR) acetonide-acetates are formed in a roughly 1:1 ratio. This result is most consistent with an all *syn* hydroxyl arrangement in the natural product.
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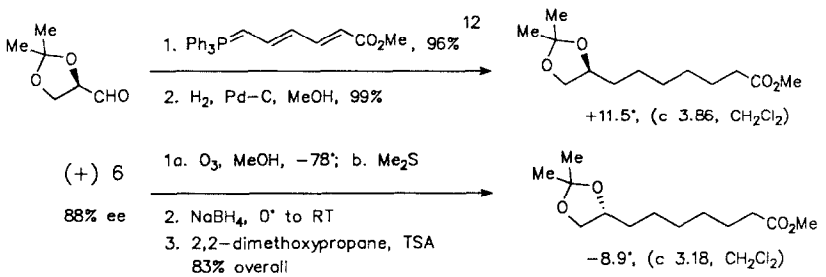
10. Diethyl tartrate was used instead of the preferred diisopropyl esters due to initial sluggish rates observed with the latter when used in dilute reaction media.
11. More proximal ester functionality on an epoxidation substrate has been reported to interfere with asymmetric epoxidation, Pridgen, L. W.; Shilcrat, S. C.; Lantos L. *Tetrahedron Lett.* **1984**, *27*, 2835. Because of this possibility, it was crucial to ascertain *both* the enantiomeric excess *and* the absolute configuration of the residual olefin regardless of the large body of precedent established for the Sharpless epoxidation. Olefin **6** was correlated with substance of known absolute stereochemistry as shown below:



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13. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399; Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
14. Reduction of ∝-epoxy-ketones with zinc borohydride produces *erythro* epoxy-alcohols. Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723; Banfi, S.; Colonna, S.; Molinari, H. M. *Syn. Comm.* **1983**, *13*, 901.
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16. For another way to achieve this transformation that was unsuccessful in the present case see Palazón, J. M.; Añorbe, B.; Martín, V. S. *Tetrahedron Lett.* **1986**, *27*, 4987.
17. **(+)-12**: $[\alpha]_D = +1.5°$ (c 0.8, CH_2Cl_2); **(-)-12**: $[\alpha]_D = -3.2°$ (c 2.14, CH_2Cl_2).
18. Synthetic **(-)-13**: $[\alpha]_D = -35.8°$ (c 1.473, CH_2Cl_2); natural **(-)-13**: $[\alpha]_D = -48.7°$ (c 1.636, CH_2Cl_2).
19. The phenyl urethane derived from epoxy-alcohol **14** is capable of forming an all pseudoequatorial 6-membered cylic carbonate. If the transition state for the epoxide opening reaction is at all product related, one would expect this to occur with the greatest facility for this isomer.

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