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SYNTHESIS OF L-660,631 METHYL ESTER AND RELATED COMPOUNDS

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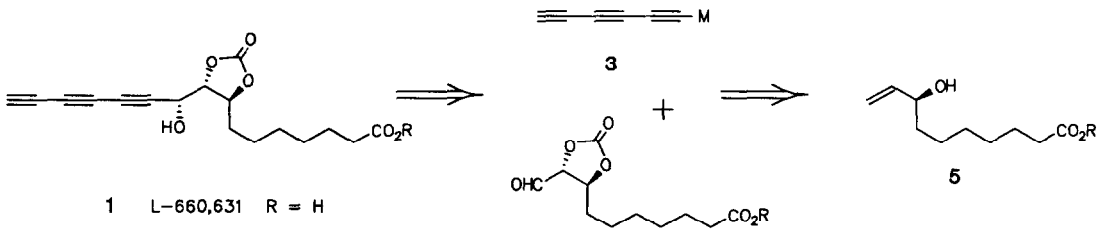
Summary: Triyne carbonate L-660,631 methyl ester (**2**) was synthesized in eight steps from cyclooctene. Synthetic methodology to permit systematic variation of the triyne portion of the molecule has been developed.

Triyne carbonate L-660,631 (**1**) is a novel natural product obtained from *actinomycetes* fermentation, the isolation and structure determination of which has been described recently.[1] This compound is an extremely potent inhibitor of cytosolic β-ketothiolase, the initial enzyme of cholesterol biosynthesis, and may be useful in studying the mechanism of action of this important enzyme.[2] Unfortunately, such studies may be rendered more complex by the rather unstable nature of concentrated preparations of L-660,631. In order to develop compounds with enhanced stability that still retained inhibitory activity, a total synthesis of the methyl ester of L-660,631 was sought. Foremost in the design of the synthetic plan was the choice of a synthetic route that would allow for the systematic replacement of the offending 1,3,5-hexatriyne subunit with more stable fragments. This report details such a total synthesis of L-660,631 methyl ester (**2**).

Retrosynthetic analysis suggested that simple disconnection into triyne **3** and aldehyde **4** subunits might be appropriate. Problematic in this approach would be the generation and control of the triyne anion with respect to the regioselectivity of the three possible sites of carbonyl addition to an aldehyde precursor such as **4**. The carbonate portion was indicated as potentially troublesome by the tendency of the natural product L-660,631 (**1**) to undergo hydrolysis in pH 10 buffer. Worrisome also was the prospect of the aldehyde decomposing *via* β-elimination under the strongly basic addition reaction conditions. Another obstacle was selectivity; an addition reaction as proposed is not inherently diastereoselective. Despite these substantial shortcomings, the disconnection was adopted because of its simplicity.

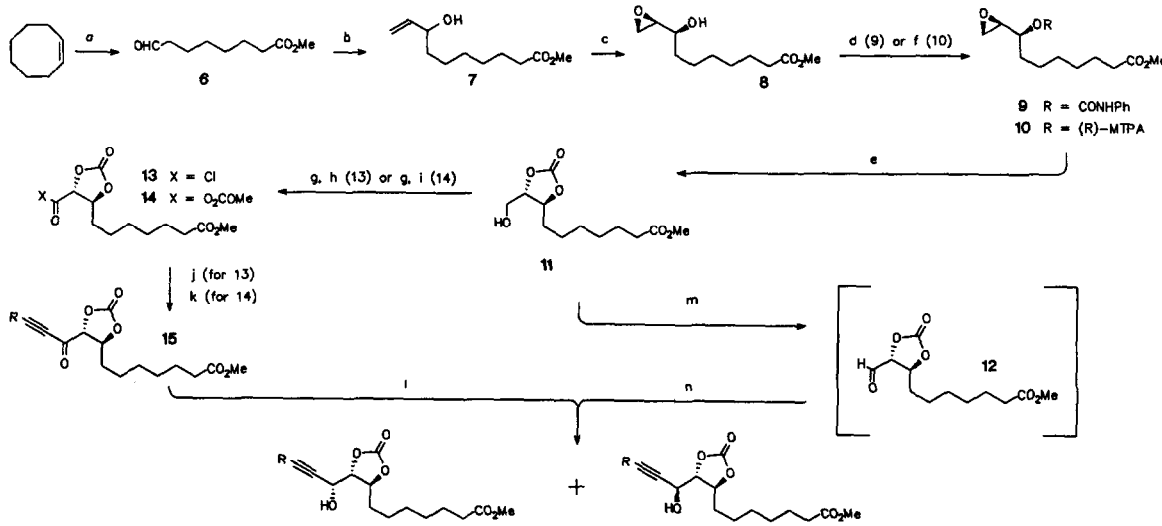


1 L-660,631 R = H

2 R = Me

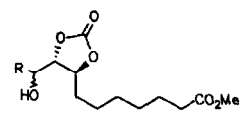
It was intended that asymmetric Sharpless kinetic resolution[3] be used to set both the absolute and the relative stereochemistry at C.8 and C.9. Earlier experiments had suggested that no interference by the terminal methyl ester functionality would occur during epoxidation of substrates such as **5**.[4] A kinetic resolution such as that intended, whereby the epoxide is the product further transformed, would only be practical in those cases where both the desired diastereoselectivity and enantioselectivity of the epoxidation process was very high. At the onset of this work, it appeared that the desired epoxidation of **5** might be expected be in the range >95% by comparison with published examples for both enantiomeric and diastereomeric selection.[3]

Schreiber workup of the ozonolysis product of cyclooctene in methanol provided methyl 7-formylhepanoate (**6**) in reasonable yield.[5,6] Selective addition of vinyl magnesium bromide to aldehyde **6** could be accomplished in THF at -78°C. In this manner, allylic alcohol **7** could be prepared in large quantities from simple and inexpensive precursors.



Reaction conditions: a)i. O_3, MeOH, CH_2Cl_2, -78°C; ii. Ac_2O, NEt_3, PhH, 77%. b) CH_2=CHMgBr, THF, -78°C, 68%. c) $Ti(O/Pr)_4$, L-(+)-DIPT, $tBuOOH$, 3Å sieves, CH_2Cl_2, -20°C to RT, 36% (72% of theoretical). d) PhNCO, MeCN, RT, 1 week, 66%. e) BF_3·OEt_2, Et_2O, -20°, 69%. f) (R)-MTPA-Cl, pyridine, CH_2Cl_2, RT, 73%. g) CrO_3, H_2SO_4, acetone, RT, 95%. h) $(COCl)_2$, CH_2Cl_2, RT. i)i. $nBuLi$, THF; ii. $ClCO_2Me$. j) CuC≡CR, LiI, Et_2O, RT. k) $LiBF_3C$≡CR, THF, -78°C. l) $NaBH_4$, MeOH, RT. m)i. $(COCl)_2$, DMSO, THF, -60 to -35°C; ii. **12**, -60 to -35°C; iii. NEt_3, -35°C to RT. n) LiC≡CR, THF, -78°C.

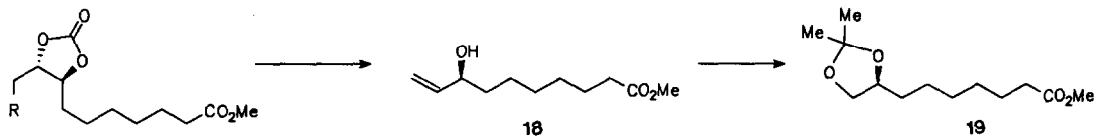
Table: Syntheses of propargylic alcohols related to L-660,631.



R		Method	Yield [18]	Ratio (α:β) [19]
Ph-	20 [20]	A	13.2%	1:1
Me_3Si-	21	C	46%	1:3
nBu-	22 [20]	A	9.0%	1:1
nBu-	22	B	3.4%	1:1
nBu-	22	C	59%	1.8:1
H-	23 [20]	A	22%	1:1
Me_3Si-	24 [21]	C	90%	~1:2
H-	25 [22]	B	1.8%	1:1
Me_3Si-	26 [23]	C	20%	1:2.5
Me-	27 [23]	C	46%	1:1.2
Me_3Si-	28 [23]	C	39%	1:1.8
Me_3C-	30 [23]	C	54%	1:2.9

Asymmetric epoxidation of **7** afforded epoxy-alcohol **8** using modified Sharpless conditions.[7] Alcohol **8** could be transformed into phenyl urethane **9** by extended treatment with phenyl isocyanate in acetonitrile. The epoxy-urethane **9** was rearranged uneventfully with cold boron trifluoride etherate in the usual manner, affording hydroxycarbonate **11** in good yield.[8]

Determination of the extent of enantiomeric excess obtained during the epoxidation step was accomplished by reaction of both racemic and resolved epoxy-alcohols **8** with R-(+)-MTPA chloride.[9,10] Examination of the 300 MHz ^{1}H NMR spectrum of **10** verified that the desired resolved material was >95% ee. In order to check that the asymmetric epoxidation had occurred in the proper absolute sense, hydroxycarbonate **11** was correlated with a substance of known absolute configuration. Conversion of **11** to the bromide **17** followed by reductive vicinal elimination produced allylic alcohol **18**.[11] Ozonolysis, reduction, and acetonide formation provided acetonide **19** which had an optical rotation identical to that of the same compound prepared from R-glyceraldehyde.[12]



11 R = OH
17 R = Br

18 **19**

Oxidation of hydroxycarbonate **11** proved more difficult than originally anticipated. Oxidation with mild Cr(VI) reagents such as PCC or PDC produced only unsaturated aldehyde products derived from β-elimination. Swern oxidation[13] was more successful, but the aldehyde product proved to be insufficiently robust to survive aqueous workup and chromatographic purification. Oxidation with Jones reagent in acetone was successful, and the crude acid product could be converted directly to acid chloride **13** by treatment with oxalyl chloride. Reaction of acid chloride **13** with isolated copper-(I) acetylides led to poor but reproducible yields of acetylenic ketones **15**. These ketones could be reduced in a nonspecific manner with sodium borohydride to afford moderate yields of the desired alcohols **16** (method A). Slightly more versatile was treatment of the mixed anhydride **14** with lithium trifluoroborate organoalkyls[14] followed by nonselective reduction as before (method B).

In order to circumvent the instability of aldehyde **12**, additions of organolithiums directly to the oxidation reaction mixture were investigated. Initial attempts to react aldehyde **12**, obtained from Swern oxidation of **11** in diethyl ether, *in situ* with various organometallic reagents were not successful. However, the desired addition products were obtained in reasonable yields when the Swern oxidation and subsequent *in situ* reaction with alkyl lithiums was carried out in THF (method C).[15] In this manner, 1-lithiohexyne could be reacted with **12** to afford a 59% yield of a 1.8:1 α:β C.10 mixture (by 300 MHz ^{1}H NMR) of diastereomers **16** [R = C≡C(CH$_2$)$_3$Me, (**22**, see TABLE)]. A summary of results for the construction of similar systems by use of these three methods is shown in the TABLE.

Formation of 1-lithio diynes *via* methyl lithium-lithium bromide complex desilylation of 1,4-*bis*-trimethylsilyl-1,3-butadiyne has been reported.[16] Straightforward application of this concept was utilized in the formation of 1-lithio-1,3,5-hexatriynes. Thus, when 1,6-*bis*-trimethylsilyl-1,3,5-hexatriyne was treated with one equivalent of methyl lithium-lithium bromide complex, a solution of the desired monoanion could be obtained. This monoanion reacts with simple aldehydes in a straightforward manner to give the expected addition products in high yields. Application toward the synthesis of L-660,631 methyl ester (**2**) was demonstrated by facile reaction with aldehyde **12** to provide trimethylsilyl capped triyne carbonate **28**. This compound is reasonably stable at room temperature in concentrated form and has been stored for several weeks at -20°C without loss of activity. Exposure to tetrabutyl ammonium fluoride-acetic acid in THF afforded L-660,631 methyl ester (**2**) in 80% yield, identical to naturally derived material in all respects examined.[17]

Biological evaluation of compounds **20** to **30** as inhibitors of mammalian β-ketothiolase will be the subject of a future report from these laboratories. The chemical instability of compounds bearing uncapped polyacetylenes is marked relative to the others, and it should prove interesting to determine whether this property correlates with inhibitory activity. A detailed understanding of the mechanism of action of the unique triyne functional group will have to await these further studies.

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10. Racemic *erythro* epoxy-alcohol **8** was prepared by treatment of racemic allylic alcohol **7** as follows: a) MCPBA, CH_2Cl_2, reflux, 95%; b)i. PDC, 3Å molecular sieves, HOAc, CH_2Cl_2, RT; ii. $ZnBH_4$, Et_2O, 0°C, 44% overall.
11. Alcohol **11** was treated with Ph_3P and CBr_4 in CH_2Cl_2 to afford bromide **17** (92% yield) and was reductively eliminated with zinc metal, HCl, and NaI in dioxane followed by esterification of demethylated compound with diazomethane to afford **18** in quantitative yield.
12. Synthetic **19**: $[\alpha]_D = +11.2°$ (c 3.44, CH_2Cl_2); natural **19**: $[\alpha]_D = +11.05°$ (c 3.86, CH_2Cl_2). See ref 1.
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17. Selected data for **2**: 300 MHz ^1H NMR ($CDCl_3$): δ 2.207 (1H, s), δ 2.321 (2H, t, J = 7.5 Hz), δ 2.862 (1H, d, J = 5.4 Hz), δ 3.675 (3H, s), δ 4.323 (1H, t, J = 4.9 Hz), δ 4.628 (1H, q, J = 5.8 Hz), δ 4.639 (1H, t, J = 5.0 Hz); IR ($CDCl_3$): 2250, 1805, 1726 cm^{-1}; $[\alpha]_D = -41.2°$ (c 0.23, $CDCl_3$).
18. All yields are those of isolated products.
19. Ratios determined by 300 MHz ^1H NMR or by quantities of isolated products.
20. Copper acetylides were synthesized by adding the appropriate alkyne in EtOH to a solution of freshly prepared $Cu(I)_2SO_4$ (from $CuSO_4$ 5 H_2O, NH_4OH, H_2O and $H_2NOH{\cdot}HCl$). The precipitate was filtered and washed well with H_2O, EtOH, and Et_2O, and dried *in vacuo*. Caution is advised as copper acetylides are known to be explosive.
21. The lithium acetylide was formed by addition of 2 equivalents of *n*BuLi to 1-(2,2-dibromoethenyl)-4-trimethylsilylethynyl benzene in THF at -78°C. This compound was prepared from 4-iodobenzaldehyde as follows: a) trimethylsilyl acetylene, cat. $(Ph_3P)_2PdCl_2$, diethylamine, cat. CuI, RT, 87%. b) Ph_3P, CBr_4, CH_2Cl_2, 0°C, 87%. See Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627 for related work.
22. The boron reagent was derived from 1-lithio-trimethylsilylbutadiyne (see ref 14). The terminal trimethylsilyl group is cleaved by $NaBH_4$ during the reduction step.
23. The lithium acetylides were prepared by treatment with MeLi LiBr complex in THF at -78 to 0°C for triynes. See ref 14 for the diyne cases.

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