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Total Synthesis of (+)-13,14-*threo*-Densicomacin

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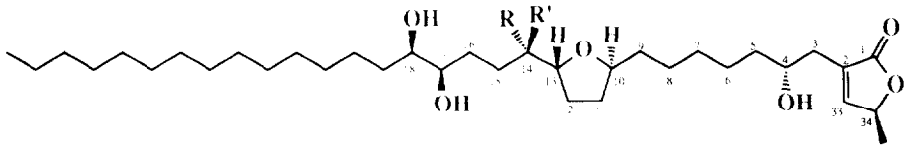
Abstract: The title compound was synthesized from propargyl alcohol and L-glutamic acid *via* a convergent approach using Sharpless asymmetric epoxidation and asymmetric dihydroxylation for the introduction of chiral centers and Pd^0-catalyzed coupling for construction of the carbon skeleton.

Annonaceous polyketides characterized by tetrahydrofuran rings and a butenolide moiety were isolated from *Annonaceae* species and attracted extensive attention in recent years because of their biological activities.[1] Several total syntheses have been reported.[2,3] Pd^0-mediated coupling of a terminal alkyne and a vinyl bromide was employed as an effective approach to the construction of the carbon skeleton.[3b]

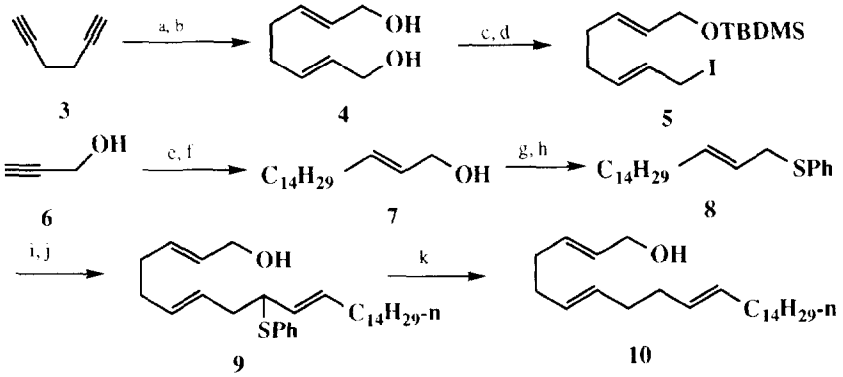
Densicomacin was isolated in our laboratory from the stem bark of *Annona densicoma* as a mixture of two stereoisomers **1** and **2**.[4] Compounds **1** and **2** exhibited potent cytotoxicity to human tumor cell in culture and represented the first two examples of C_{35} polyketides with a tetrahydrofuran ring located between C(10) and C(13). The complete stereochemistry of all seven carbinol centers has been assigned by using ^1H chemical shift patterns of Mosher ester derivatives.[5] The configuration of the carbinol center at C(14) is *S* and *R* for **1** and **2** respectively. We herein wish to report the total synthesis of (+)-13, 14-*threo*-densicomacin (**2**).



1, R=OH, R'=H,13,14-*erythro*. **2**, R=H, R'=OH, 13, 14-*threo*

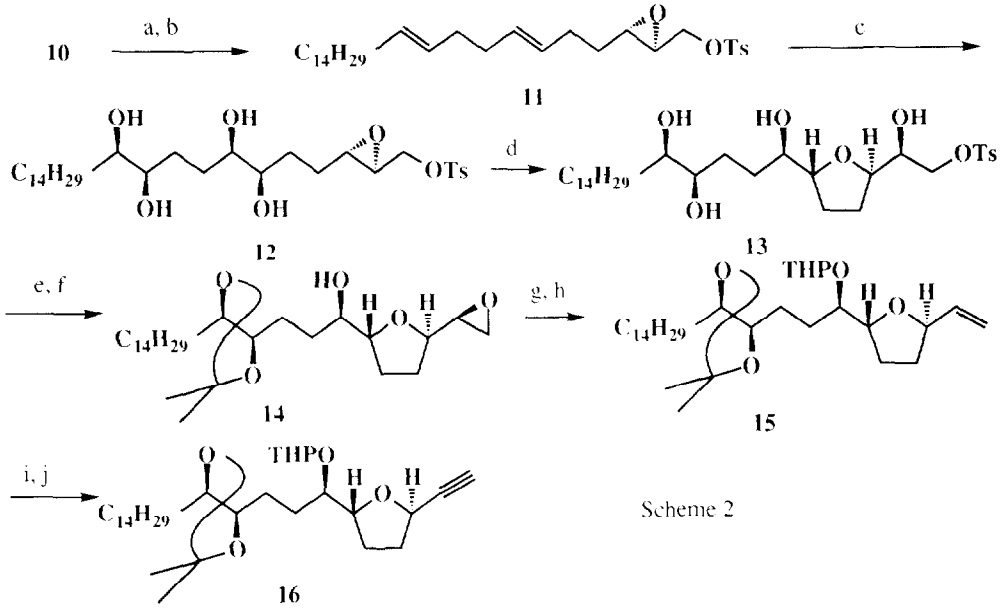
The key intermediate *E*, *E*, *E*-trienol **10** was prepared *via* a multi-step process as shown in Scheme 1. Diyne **3** was treated with $BuLi/(CH_2O)_n$ and then the triple bonds were reduced to give *E*,*E*-diendiol **4**.[6] Monosilylation of diol **4** was followed by conversion of allylic alcohol to allylic iodide **5**. Compound **8** was synthsized *via* a four-step sequence: alkylation of propargyl alcohol **6** was followed by reduction of the propargyl alcohol derivative to allylic alcohol **7**; displacement of the hydroxyl group with a phenylthio group was achieved *via* an intermediate bromide. The coupling reaction of α-phenylthio carbanion with iodide **5** yielded alcohol **9** after desilylation. The phenylthio group was removed by $Li\text{-}NH_3$[7] to afford *E*,*E*,*E*-trienol **10** without double bond isomerization and migration. An alternative approach to **10** is also described in Scheme 5.[8]

Scheme 1



a, 1) n-BuLi, -78 °C to -20 °C, 1 h; 2) $(CH_2O)_n$, -20 °C, 2 h, 20 °C, overnight, 80%; b, $LiAlH_4$, THF, reflux, 1 h, 78%; c, TBDMSCl, imidazole, DMF, 20 °C, overnight, 75%; d, Ph_3P-I_2, Imidazole, 0 °C, 45 min, 82%; e, 1), n-BuLi, THF, -78 °C to -20 °C, 1 h; 2) $C_{14}H_{29}Br$, HMPA, 20 °C, overnight, 95%; f, $LiAlH_4$, THF, 3 h, 20 °C, 92% ; g, PBr_3, ether, 0 °C, 1 h, 91%; h, PhSLi, THF-HMPA, 20 °C, 2 h, 92%; i, 1) BuLi, -20 °C 1 h; 2) **5**, 20 °C; j, TBAF, THF, 0 °C, 1 h, 87% for 2 steps; k, Li-NH_3 /NaH, -35 °C, 3 h, 86%

The absolute stereochemistry of the five carbinol centers at C(10), C(13), C(14), C(17) and C(18) was established using Sharpless asymmetric epoxidation and asymmetric dihydroxylation methods. Asymmetric epoxidation[9] of **10** followed by tosylation of the epoxyalcohol gave tosylate **11**. Double asymmetric dihydroxylation[10] of the diene resulted in tetraol **12**. The THF ring was formed in the presence of acid with concomitant epoxide ring opening to give a new tetraol **13**. The vicinal diol was acetonized and the corresponding tosylate was converted to the epoxide **14** by treatment with K_2CO_3. Protection of the

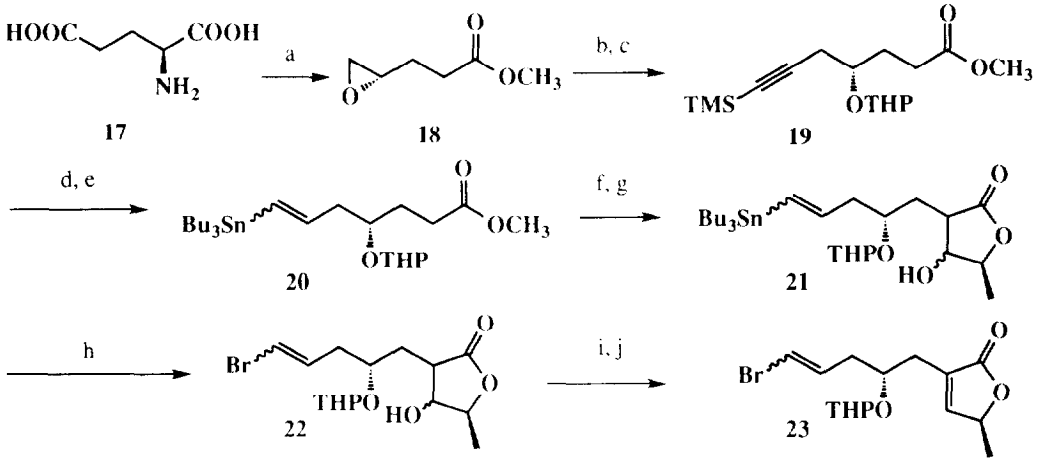


Scheme 2

a, Ti(Oi-Pr)4, L-DET, t-BuOOH, CH_2Cl_2, -20 °C, 6 h, 94%; b, *p*-TsCl, Pyridine, 80%, 0 °C, overnight; c, AD-Mix-β, 0 °C, 24 h, 91%; d, CSA, CH_2Cl_2, 20 °C, 1 h, 92%; e, $Me_2C(OMe)_2$, CSA, 1 h, 90%; f, K_2CO_3, MeOH, 1 h, 89%; g, DHP, PPTS, 4 h, 94%; h, PBu_3, 160 °C, 66%; i, Br_2, CCl_4, 0 °C, 0.5 h, 90%; j, LDA/THF, -78 °C, 1 h, 89%.

hydroxylgroup as a tetrahydropyranyl ether, followed by deoxygenation of the epoxide with PBu_3[11], afforded olefin **15**. The alkene was converted to alkyne **16** by bromination and then dehydrobromination.

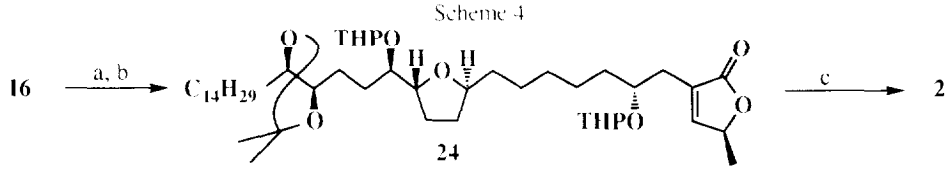
Scheme 3



a, (i) $NaNO_2$, H_2SO_4; (ii), $BH_3 \cdot SMe_2$, THF; (iii), TsCl, Py; (iv), NaI, acetone, reflux; (v), K_2CO_3, MeOH; b, 1) TMSC≡CH, BuLi, -78 °, 15 min; 2) $BF_3 \cdot OEt_2$, -78 °, 15 min, 3) **18**, - 78 °, 0.5 h; 83%; c, DHP, PPTS, 20 °, 4 h, 92%; d, TBAF, THF, 0 °, 1 h, 90%; e, Bu_3SnH/AIBN, 160 °, 4 h, 80%, f, 1) LDA, -78 °, 0.5 h; 2) O-MTM-(S)-lactal, -78 °, 3 h; 82%; g, MeI, $NaHCO_3$, acetone-H_2O, reflux, overnight, 86%; h, Br_2, CCl_4, -20 °, 0.5 h, 92%, i, $MeSO_2Cl$, Et_3N, -20 °, 0.5 h, then DBU, 20 °, 4 h, 54%.

The preparation of the butenolide is shown in Scheme 3. L-Glutamic acid was converted to epoxide **18** by a five-step sequence according to the literature.[12] Lithium trimethylsilylacetylide was treated with $BF_3 \cdot OEt_2$ and epoxide **18**, after protection of the hydroxyl group with DHP as a THP ether, to afford **19**. Desilylation gave a terminal alkyne, which was converted to the vinyltin compound **20** by reduction with n-Bu_3SnH.[13] Lactone **21** was obtained by aldol condensation between the enolate of **20** and methylthiomethyl protected (S)-lactal followed by the deprotection and lactonization in the presence of MeI/$NaHCO_3$. Reaction of the compound **21** with bromine afforded vinyl bromide **22**. The butenolide functionality was constructed by mesylation of the hydroxyl group and elimination to afford vinyl bromide **23**,[14] one of the coupling precursors.

Scheme 4



a, **23**, $Pd(PPh_3)_4$, CuI, Et_2NH, 20 °, 14 h, 80%; b, $(PPh_3)_3RhCl$, PhH, 20 °, 4 h, 85%; c, CSA, MeOH, 20 °, 8 h, 81%.

The carbon skeleton was constructed by Pd^0-mediated coupling of the alkyne **16** and the vinyl bromide **23**, after selective hydrogenation mediated by Wilkinson's catalyst,[3b, 15] to afford **24**. Deprotection gave the title compound **2**. The synthetic compound **2** gave an R_f value and a ^1H NMR spectrum consistent with those from the authentic sample. The specific rotation of synthetic compound **2** was $[a]_D^{20}$ =+20.4 (c=0.26,

MeOH)[16] which was lower than that of the natural densicomacin (as a mixture of **1** and **2**), $[a]_D^{20}$ =+26 (c=0.05 , MeOH)[3]. Thus, the asymmetric synthesis of densicomacin **2** was achieved. The further application of this methodology to the synthesis of densicomacin analogs for structure-activity relationship evaluation against human cell lines in culture is underway.

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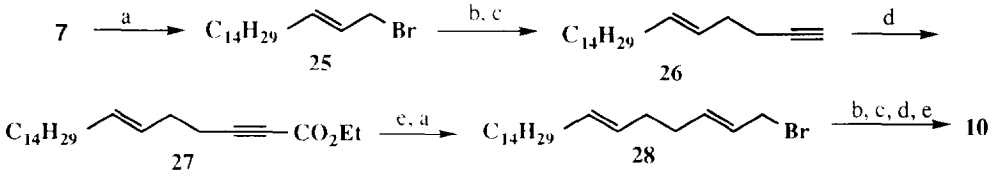
8. An alternative approach to *E,E,E*-trienol **10**: Bromide **25** from allylic alcohol **7** coupled with the anion of 1-trimethylsilylpropyne (92%), after desilyation with TBAF (95%), to afford enyne **26**. Compound **26** was treated with BuLi and then ethyl chloroformate to afford ester **27** (93%). LAH reduction of the riple bond and ester (92%), followed by bromination (92%), afforded allylic bromide **28**. Repeating of steps b, c, d and e afforded *E,E,E*-trienol **10** in 72% overall yield.

Scheme 5



a, PBr_3; b, TMS-C≡C-CH_2-Li; c, TBAF; d, BuLi/$ClCO_2Et$; e, $LiAlH_4$, THF, reflux, 1 h.

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16. In $CHCl_3$; synthetic sample 2, $[a]_D^{20}$ =+10 (c=0.26); authentic sample, $[a]_D^{20}$ =+7.8 (c=0.62).

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