Tetrahedron Letters, Vol. 35, No. 1, pp. 157-160, 1994
Printed in Great Britain

0040-4039/94 $6.00 + .00
Pergamon Press Ltd

Total Synthesis of (10ξ,15R,16S,19S,20S,34R)-Corossoline

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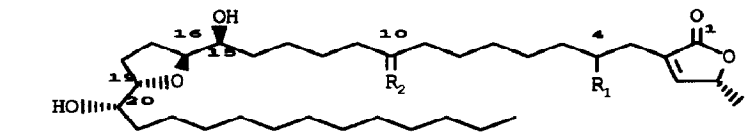
Abstract (10ξ,15R,16S,19S,20S,34R)-Corossoline, a structural representative of the cytotoxic monotetrahydrofuranyl annonaceous acetogenins, was synthesized from two chiral starting materials -- (S)-glutamic acid and (R)-ethyl lactate, and 10-undecenoic acid.

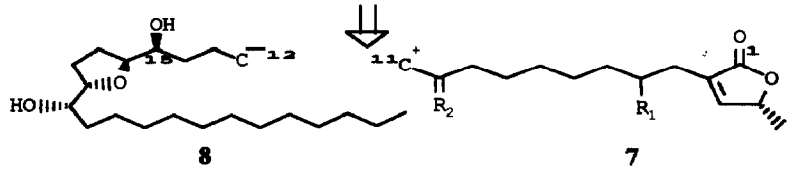
Nearly ninety members of annonaceous acetogenins characterized by one or two tetrahydrofuran ring and a methylated γ-lactone have been isolated from *Annonaceae* species[1] since the first example in 1982[2], among which about thirty members possess one monotetrahydrofuran ring. Annonaceous acetogenin exhibit a broad spectrum of potent biological activities (cytotoxic, antitumoral, antimalarial, antimicrobial, immunosuppressive, antifeedant, and pesticidal). Recently it has been attracted great attention that some members among them showed much more potential antitumor activity than that of those famous antitumor agents, such as adriamycin and taxol[3]. The biological property and the stereochemistry, which was hardly elucidated from such waxy compounds, prompted chemists to deal with the organic syntheses of these acetogenins and their analogues. The first synthesis of (+)-(15, 16, 19, 20, 23, 24)-hexepi-uvaricin, a bis-tetrahydrfuranyl acetogenin analogue, was reported by Hoye et al.[4] one year ago, and the synthesis[5] of muricatacin, the simplest annonaceous acetogenin, and a few syntheses[6] of their segments were also published since 1992. Herein we communicate our primary effort in the enantioselective synthesis of mono-tetrahydrofuranyl annonaceous acetogenin structure.

Apparently derived from the polyketide pathway, many of the acetogenins have the similar structural character. For example, six mono-tetrahydrofuranyl acetogenins, solamin **1**, murisoline **2**, corossolone **3**, corossoline **4**, annonacinone **5**, and annonacin **6**, have a C35 skeleton and a common C_{12}-C_{32} segment with stereochemistry proposed as threo-trans-threo at C_{15}, C_{16}, C_{19}, C_{20}. From the retrosynthetic perspective, these acetogenins could be disconnected into two segments **7** and **8**, from which only the segment **7** is different each other. Therefore all the six acetogenins could in principle be synthesized from a common segment **8** contained the tetrahydrofuran ring and an individual C_1-C_{11} segment **7** (Figure 1).

Preparation of 8A from glutamic acid. The well known chiron **9** prepared from L-glutamic acid[7] was chosen as the chiral pool. **9** was treated with benzyl bromide and silver oxide in DMF[8] to give the protected compound **10** in 83% yield. Reduction of **10** with DIBAL followed by Wittig reaction with CH_2=PPh_3 in benzene afforded **11** in 49% yield. Iodoetherification of **11** with I_2 and $NaHCO_3$ in acetonitrile gave a 5:1 mixture of diastereoisomers favored trans isomer **12** in 50% yield. Treatment of **12** with $Et_4N^+OAc^-$ in DMF at 60°C followed by hydrolysis of the formed acetate gave alcohol **13** in 67% yield. Grignard reaction at -20°C of the crude aldehyde collected from Swern's oxidation of **13** produced threo **14** and erythro **15** in 3:1 ratio and 67% total yield. **15** could be converted to **14** in 51% yield (ratio of **14**:**15**=7.3:1) by Jone's oxidation and L-selectride® reduction subseqently. After acetylation and hydrogenolysis of **14**, the resulting alcohol **16**

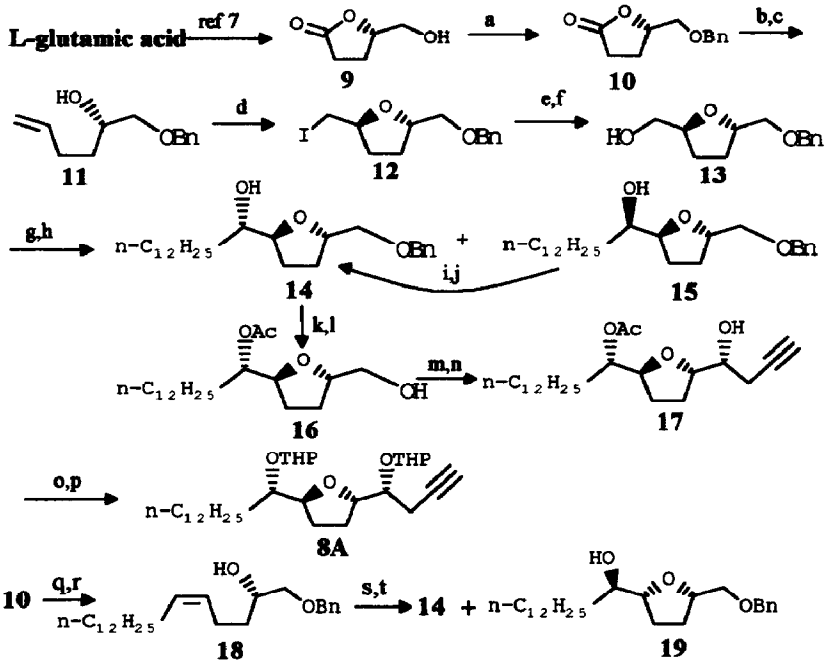


	R_1	R_2		R_1	R_2
1 Solamin	H	H, H	4 Corossoline	H	H, OH
2 Murisoline	OH	H, H	5 Annonacinone	OH	O
3 Corossolone	H	O	6 Annonacin	OH	H, OH



8 **7**

Figure 1

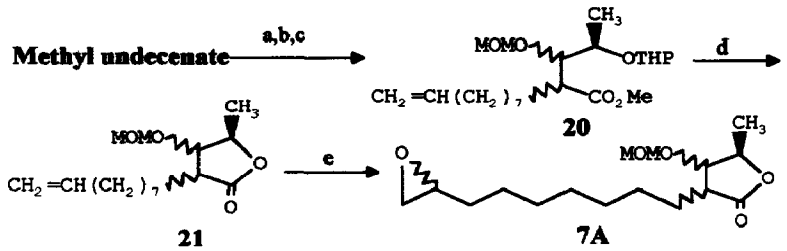


Scheme 1. reagents and conditions: a) Ag_2O, BnBr, 83%; b) DIBAL; c) CH_2=PPh_3, 49%; d) I_2, $NaHCO_3$, 50%, 5:1diastereoselectivity favored trans isomer; e) $Et_4N^+OAc^-$, 67%; f) K_2CO_3, 100%; g) Swern's oxidation; h) n-$C_{12}H_{25}MgBr$, -20°C, 67%, 14/15 = 3/1; i) Jone's oxidation; j) L-selectride®, 51%; k) Ac_2O, Py, 98%; l) H_2, Pd-C, 96%; m) Swern's oxidation; n) Zn, propargyl bromide, DMF-Et_2O(1:1), 65%, 8.3:1 diastereoselectivity favored 17; o) K_2CO_3, 100%; p) DHP, PPTS, 98%; q) DIBAL; r) n-$C_{12}H_{25}CH$=PPh_3, 33% from 10; s) MCPBA; t) pTsOH, 66%, 14/19 = 6.6:1.

was oxidized to the corresponding aldehyde by Swern's method. Barbier reaction of the aldehyde with propargyl bromide in the presence of zinc dust in DMF -ether (1:1) gave threo-trans-erythro (C-20/C-19/C-16/C-15) **17** in 65% yield (8.3:1 diastereoselectivity favored **17**). Hydrolysis of **17** followed by THP etherification afforded protected C_{12}-C_{32} segment **8A** in 98% yield.

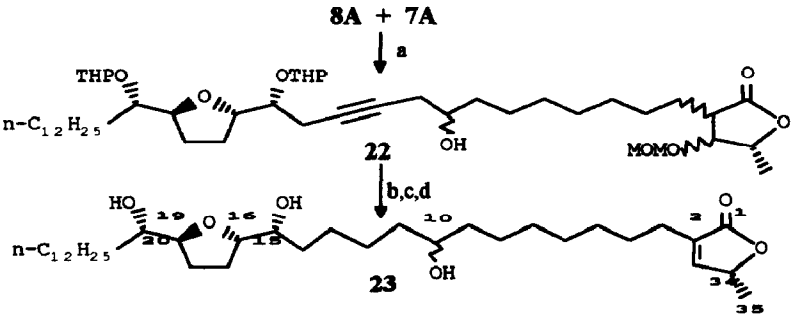
We also obtained the key precursor **14** in 66% yield and 6.6:1 trans/cis selectivity from compound **18**, which was from **10** in 33% yield in the same way as the preparation of **11** (Scheme 1).

Preparation of 7A from undecenoic acid and D-lactic acid. Treatment of methyl undecenate with 1.1 eq. LDA and (R)-O-tetrahydropyranyl lactal gave the aldol-type product, which was converted to its MOM ether **20** in 55% overall yield as a mixture of isomers. **20** was treated with 10% H_2SO_4 in THF to afforded γ-lactone **21** quantitatively. Epoxidation of **21** with MCPBA gave C_1-C_{11} (Containing C_{33},C_{34},C_{35}) segment **7A** in 64% yield (Scheme 2).



Scheme 2. reagents and conditions: a) LDA; b) (R)-O-THP-lactal, 65%; c) MOMCl, $^iPr_2NEt$, 85%; d) 10% H_2SO_4, THF, 100%; e) MCPBA, 64%.

Conjunction of the segments and total synthesis of the title compound. Compound **8A** was treated with 1.0 eq. n-BuLi and 1.2 eq. $BF_3{\cdot}OEt_2$ in THF at -78°C, and then **7A** was added into the reaction mixture at the same temperature to give **22** in 58% yield. **22** was converted to the title compound ---(10ξ ,15R,16S,19S,20S,34R)-corossoline **23**[9] in 44% yield by hydrogenation, deprotection of THP ether and β-elimination (Scheme 3).



Scheme 3. reagents and conditions: a) n-BuLi, $BF_3{\cdot}OEt_2$, **7A**, -78°C, 58%; b) H_2, Pd-C, 100%; c) PPTS, MeOH, 76%; d) 4 eq. DBU in THF, room temperature, 4h., 68%.

In conclusion, a total synthesis of a pair of isomers of corossoline was achieved and the chiral centers, except C_{10}, in the product were under control[10]. Application of this methodology to the synthesis of natural compound and other isomers, and the bioassay of our product are under way.

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9. Spectral data of **23**: mp. 47~50°C. $[\alpha]_D^{20}$ - 23.7 (c 0.057, MeOH). UV: λmax 212nm, logε 3.93 (c 8μg/mL, MeOH). IR (FT, KBr) ν max: 3455.6, 3406.8, 2922.2, 2850.2, 1744.7, 1467.0, 1116.5, 1082.6, 1030.0, 721.4 cm^{-1}. ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 0.88 (3H, t, H-32, J=6.8Hz), 1.26~1.55 (34H, m), 1.41 (3H, d, H-35, J=6.8Hz), 1.73 (10H, m), 1.95 (2H, m), 2.27 (2H, m, H-3), 3.46 (1H, m, H-20), 3.60 (1H, m, H-10), 3.83 (2H, m, H-15&H-19), 3.91 (1H, m, H-16), 4.99 (1H, m, H-34), 6.98 (1H, m, H-33) ppm. MS (FAB, m/z): 713 [M^++Cs], 581 [MH^+], 563 [MH^+-H_2O], 545, 527, 226. Anal. calcd. for $C_{35}H_{64}O_6$: C 72.36, H 11.11. Found: C 72.38, H 11.05.
10. Satisfactory spectroscopic data, together with microanalytical and/or mass spectroscopic data were obtained for all new compounds.

(*Received in China* 26 *June* 1993; *accepted* 15 *July* 1993)