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A SIMPLE STEREOSELECTIVE SYNTHESIS OF A TETRACYCLIC C_{14} GINKGOLIDE

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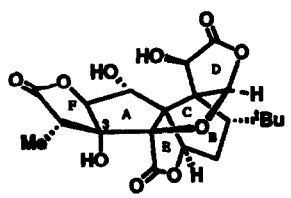
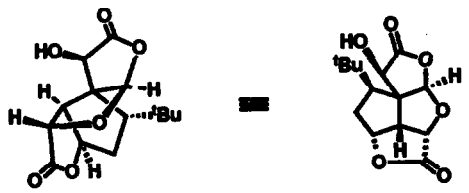
Summary: A short and efficient total synthesis of the structurally interesting tetracyclic ginkgolide derivative (±)-2 is described.

We have recently described a total synthesis of ginkgolide B (1),[1] a potent antagonist of platelet activating factor,[2] and also the application of this chemical route to the synthesis of structurally simpler analogs of 1.[3] Since certain of these synthetic analogs lacking ring F and the groups attached to C(3) showed biological activity comparable to 1 itself, the synthesis and study of the even simpler tetracyclic fourteen-carbon analog of ginkgolide B lacking rings A and F (2) became of great interest. A successful total synthesis of (±)-2 is described herein.



Ginkgolide B (1)



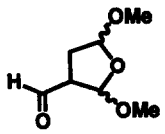
Target molecule 2

The reaction of aldehyde 3 (Aldrich Co.), ylide 4[4] and sodium hydride (2 equiv) in tetrahydrofuran (THF) containing 0.2 equiv of water at 0°C for 1 h afforded after extractive isolation and chromatography on silica gel (sgc) the *Z*-enone 5 in 72% yield.[5] Treatment of 5 with 1 equiv of tosyl azide and 1.7 equiv of Et_3N in CH_3CN at 23°C for 5 h produced the diazo derivative 6 in 97% yield. Slow addition of 6 in CH_2Cl_2 to a suspension of rhodium(II) mandelate in CH_2Cl_2 (2.5 mole %, 0.2 mM) at 23°C over 9 h resulted in formation of spiro enone 7 (73%) which upon exposure to 9.4 equiv of CH_3SO_3H in CH_2Cl_2 (0.03 M) at -10°C for 2 h and -5°C for 4 h provided the (±)-tricyclic keto lactone 8 as a single stereoisomer, mp 118-

119°C, in 78% yield. Conjugate addition of *t*-butyl to **8** was carried out using 9 equiv of a reagent prepared from *t*-BuLi and CuCN (1 : 1) in ether at -45°C for 30 min. The reagent was cooled to -78°C and treated with Me_3SiCl (2 equiv per equiv of tBuCuCNLi), and then enone **8** in THF was added slowly at -78°C. After a reaction time of 45 min at -78°C and 30 min at -45°C, the reaction mixture was neutralized with 1N aq HCl and the product **9** was isolated extractively and purified by sgc (87% yield as a single stereoisomer, mp 130-131°C). Reduction of **9** by $NaBH_4$ in ethanol at 0°C for 2 h proceeded stereospecifically to give hydroxy lactone **10**, mp 123-124°C, in 99% yield. The lactone function of **10** was reduced selectively with 2.3 equiv of diisobutylaluminum hydride in toluene at -78°C for 2 h to afford a mixture of isomeric lactols **11** (98%, ratio 3 : 1, separable by sgc, major diastereomer: mp 114-115°C, β-OH configuration), which was converted by reaction with 1.2 equiv of methanesulfonyl chloride and 3 equiv of triethylamine in CH_2Cl_2 at 0°C for 1.5 h , quenching with aq $NaHCO_3$, extractive isolation, and sgc into the lactol mesylate **12** (mp 112-113°C, 98%). Acetylation of **12** (Ac_2O, Et_3N, CH_2Cl_2, 23°C for 24 h) provided an easily separable mixture of two epimeric acetates **13** (α-OAc), mp 113-114°C, 88% and **13** (β-OAc), mp 115-116°C, 8.5%. Treatment of the α- and β-acetate mixture with 1.5 equiv of trimethylsilyl cyanide and 0.1 equiv of boron trifluoride etherate in CH_2Cl_2 at 0°C for 15 min gave, after quenching with Et_3N, extractive isolation and sgc, the α-cyano ether **14**, mp 140°C (58% yield) and the epimeric β-cyano ether (more polar by sgtlc, 40% yield).

The ring system of **2** was established simply by exposure of the α-cyano ether **14** to a mixture of 2 M aqueous $KHCO_3$ and 30% H_2O_2 in 19 : 1 MeOH-H_2O (ratio by vol 2 : 1 : 20) at 0°C for 2 h and 23°C for 18 h to give in 87% yield lactone **15**, mp 120-121°C. Elimination of methanol from **15** was effected by heating with 0.3 equiv of *p*-tosic acid in toluene at reflux for 6 h in the presence of 5A molecular sieves to afford vinyl ether **16**, mp 143-144°C, (74%). Hydroxylation of the double bond of **16** (0.05 equiv of osmium tetroxide, 1.2 equiv of trimethylamine N-oxide in 4 : 1 acetone-H_2O at 23°C for 48 h) followed by isolation of the resulting α-hydroxy acetal and oxidation with 1.8 equiv of Br_2 in 1 : 2 acetic acid-water containing sodium acetate as buffer at 0°C for 15 min and 23°C for 1 h produced the target molecule **2**, mp 253°C (after recrystallization from CH_2Cl_2-Et_2O), in 82% overall yield.[6]

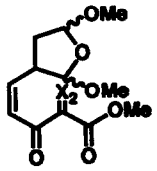
The stereochemistry of enone **8** and the adduct with tBuCuCNLi followed from by ^1H NMR NOE experiments at 500 MHz which yielded the results summarized in **17**. The stereochemical assignments to the individual diastereomers corresponding to **13** and **14** were clear from the measured vicinal coupling constants for protons in the subunits -C*H*-C*H*(OAc)- and -C*H*-C*H*(CN)- (7.2 Hz for *cis* H/H and 3.8 Hz for *trans* H/H). ^1H NMR data also confirmed fully the stereochemistry of **2**.



3

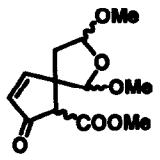
$Ph_3PCHCOCH_2COOMe$

4



5 X=H

6 X=N



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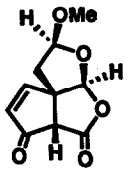

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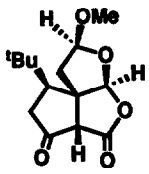

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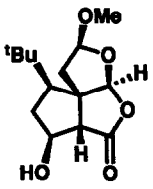

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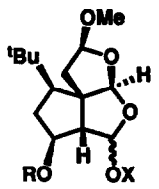
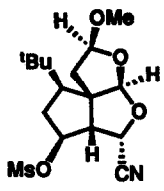


11 R=X=H

12 R=SO_2Me, X=H

13 R=SO_2Me, X=CH_3CO



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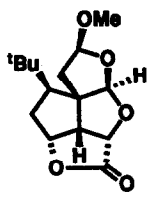
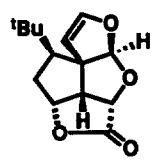


15



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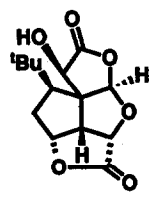

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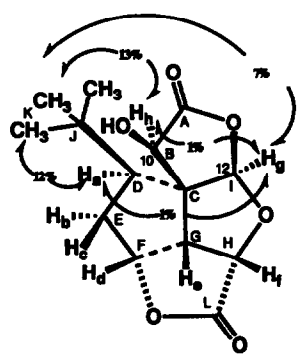

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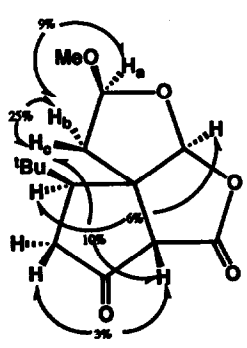

J_{ab}=4.9Hz
J_{ac}=0Hz
J_{bc}=13.1Hz

17

The synthesis of tetracyclic dilactone **2** which is outlined herein features a number of noteworthy steps and methods including the following: (1) the successful stereospecific construction of the spiro-fused ring system of **8** using a tactical combination of *cis*-Wittig olefination, carbenoid ring closure and lactonization; (2) stereospecific conjugate addition to introduce the *t*-butyl (or other carbon) appendage; and (3) a novel annulation to attach the final lactone ring.[8]

References and Notes

1. (a) E. J. Corey, M.-C. Kang, M. C. Desai, A. K. Ghosh, and I. N. Houpis, *J. Am. Chem. Soc.*, **110**, 649 (1988); (b) E. J. Corey and A. V. Gavai, *Tetrahedron Letters*, **29**, 3201 (1988); (c) E. J. Corey, *Chem. Soc. Rev.*, **17**, 111 (1988).
2. (a) D. J. Hanahan, *Ann. Rev. Biochem.*, **55**, 483 (1986); (b) K. Cooper and M. J. Parry, *Ann. Rept. Med. Chem.*, **24**, 81 (1989); (c) P. Braquet, *Drugs of the Future*, **12**, 643 (1987); (d) P. Braquet, Ed., *The Ginkgolides, Chemistry, Pharmacology and Clinical Perspectives Vol. I* (J. R. Prous Science Publishers, Barcelona, 1988).
3. E. J. Corey and A. V. Gavai, *Tetrahedron Letters*, **30**, 6959 (1989).
4. K. M. Pietrusiewicz and J. Monkiewicz, *Tetrahedron Letters*, **27**, 739 (1986).
5. Satisfactory spectroscopic data were obtained for each synthetic intermediate using chromatographically purified and homogeneous samples. All reactions involving air/moisture sensitive reactants were conducted in an inert atmosphere. Reaction products were oils unless otherwise indicated.
6. See D. F. Taber and J. L. Schuchardt, *J. Am. Chem. Soc.*, **107**, 5289 (1985) and refs. therein cited.
7. The following data are recorded for tetracyclic dilactone (±)-**2**. Rf 0.36(AcOEt:Hexane=1:1); ^{1}H NMR($CDCl_3$;500MHz), δ(ppm): 1.09(s,9H,$C(CH_3)_3$) 2.02-2.10(m,2H,H_a,H_c) 2.23(m,1H,H_b) 2.95(broad s,1H, OH) 3.84(dd,J_{ef}=9.6Hz,J_{de}=6.9Hz,1H,H_e) 4.909(s,1H,H_h) 4.912(d,J_{ef}=9.6Hz,1H,H_f) 5.93(s,1H,H_g); ($CDCl_3$-CD_3OD;500MHz), δ(ppm): 1.03(s,9H,$C(CH_3)_3$) 1.95(dd,J_{ac}=14.1Hz,J_{ab}=5.3Hz,1H,H_a) 2.05(dt like,J_{ac}=14.1Hz,J_{bc}=13.7Hz,J_{cd}=4.6Hz,1H,H_c) 2.20(dd,J_{bc}=13.7Hz,J_{ab}=5.3Hz,1H,H_b) 3.84(dd, J_{ef}=9.6Hz,J_{de}=6.9Hz,1H,H_e) 4.82(s,1H,H_h)4.84(d,J_{ef}=9.6Hz,1H,H_f) 5.00(dd,J_{de}=6.9Hz,J_{cd}=4.6Hz,1H,H_d) 5.83(s,1H,H_g); ^{13}C NMR($CDCl_3$-CD_3OD;125MHz), δ(ppm): 28.88(C_K) 31.98(C_J) 36.36(C_E) 48.58(C_D) 49.82(C_G) 67.24(C_C) 69.91(C_B) 79.93(C_F) 81.04(C_H) 108.43(C_I) 172.89(C_A) 174.21(C_L); IR(neat) 3441, 1775, 1757, 1369, 1251, 1131, 1093, 1008, 993, 968, 950, 935, 884, 735, 688, 668 cm^{-1}.
8. This research was supported by grants from the National Institutes of Health, the National Science Foundation, and the Uehara Foundation.

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