Tetrahedron Letters, Vol.32, No.36, pp 4623-4626, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

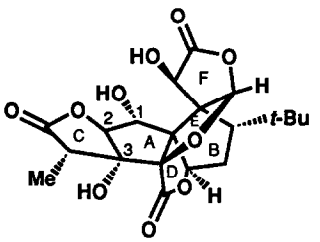
Enantioselective Total Synthesis of Ginkgolide Derivatives Lacking the *tert*-Butyl Group, an Essential Structural Subunit for Antagonism of Platelet Activating Factor

E. J. Corey and K. Srinivas Rao

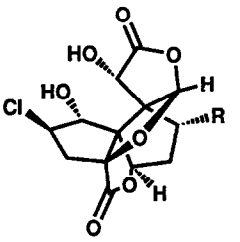
Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: An enantioselective total synthesis of the ginkgolide B analog 3 is reported along with the results of bioassays for antagonism of platelet activating factor. The three orders of magnitude difference in bioactivity of 2 and 3 demonstrates that the tert-butyl group of the ginkgolides is essential for anti-PAF potency.

Platelet activating factor (PAF), considered to be a mediator of conditions such as allergy, inflammation and tissue rejection, is antagonized by ginkgolide B (**1**) (IC_{50} *ca.* 0.6 μM).[1] We recently demonstrated[2] that a number of simpler structural analogs of **1** which lack the lactone ring C (attached to C(2) and C(3) are almost as potent as PAF antagonists, for example (±) **2**, IC_{50} 1.1 μM.[2] Certain parts of the ginkgolide B structure, however, are clearly critical to anti-PAF activity, e.g. rings E and F. In this paper we report on the enantioselective synthesis of the ginkgolide analog **3**, lacking the *tert*-butyl substituent on ring B and the question of the role of that substituent in the anti-PAF activity of the ginkgolides.



1

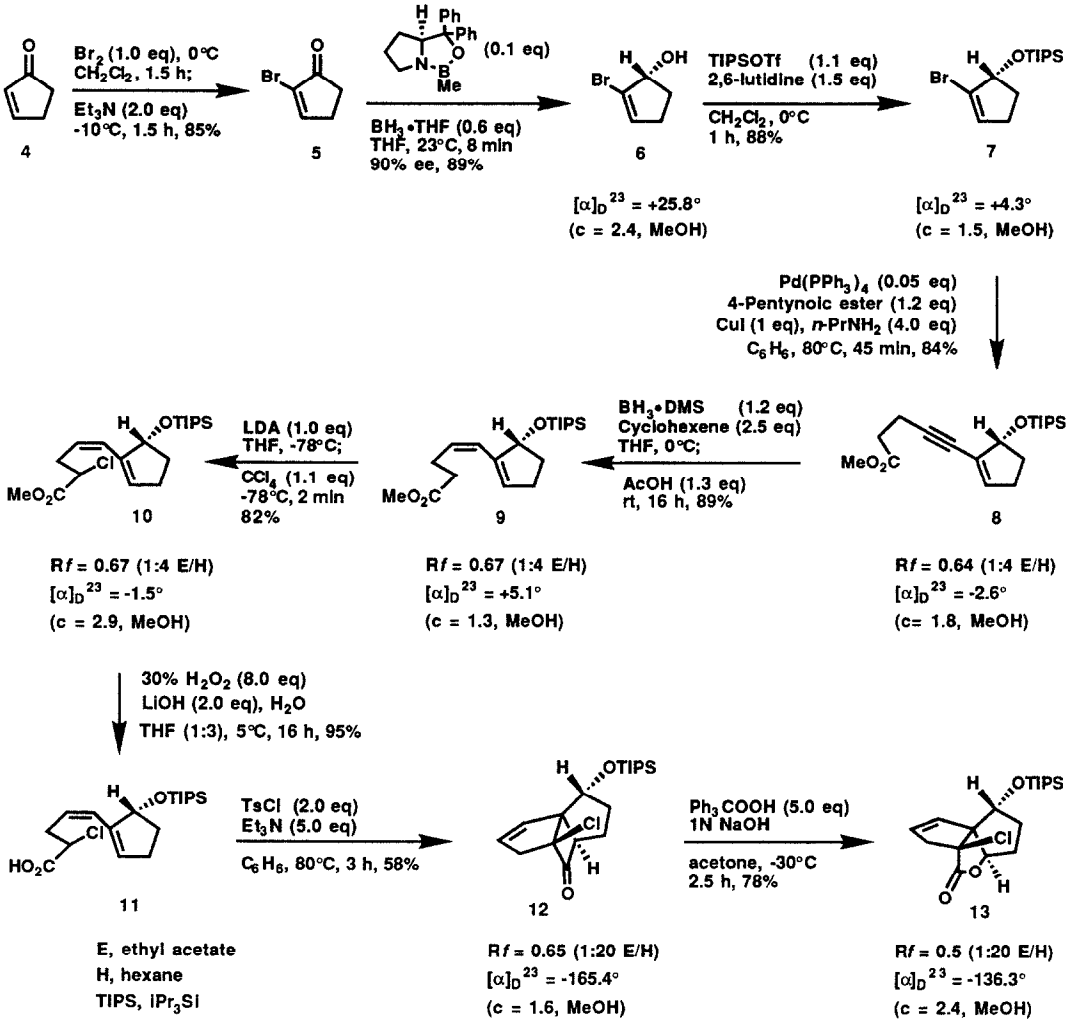


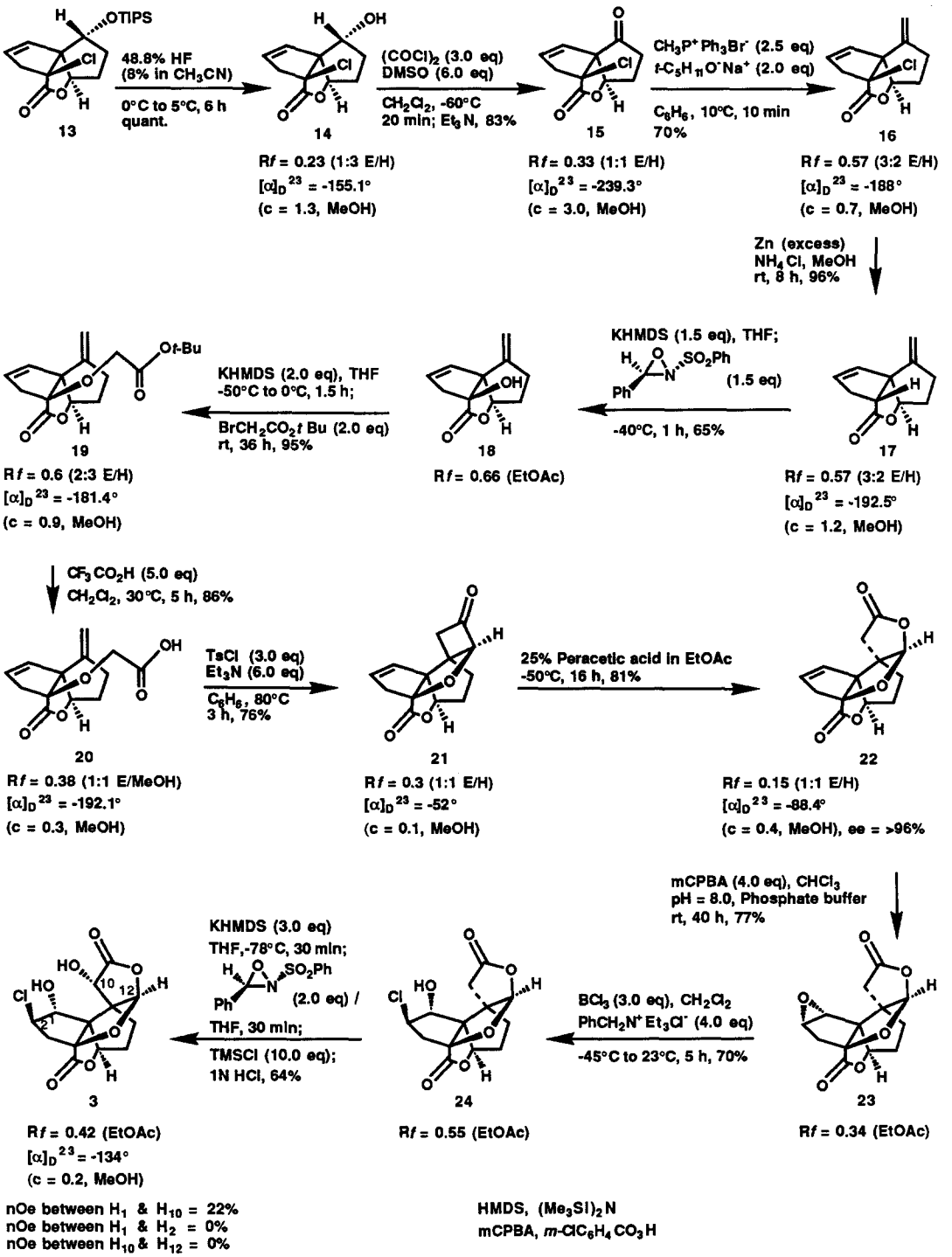
2 R = *t*-Bu
3 R = H

The synthetic route to **3** is outlined in the accompanying flow chart which includes reaction conditions and yields. The first chiral intermediate (**6**) was produced from the achiral precursor **5** by oxazaborolidine-catalyzed reduction[3] with 95 : 5 enantioselectivity. Double annulation to produce the tricyclic ketone **12** was accomplished by a modification of the methodology employed for the synthesis of ginkgolide B[4] utilizing a novel α-chloroketene.[5] The next two rings were also formed in one step by an interesting position specific intramolecular α-oxaketene-olefin [2 + 2]-cycloaddition which transformed **20** into pentacyclic intermediate **21**. Each of the key Baeyer-Villiger steps, **12** → **13** and **21** → **22**, was position specific. The intermediate **22**, mp 116-117°, was obtained in > 96% enantiomeric excess, as

shown by HPLC analysis using a Daicel OD column, after recrystallization. Conversion of **22** to the desired target **3** was accomplished in three steps, as shown. The stereochemistry of **3** was confirmed by ^{1}H NMR NOE experiments at 500 MHz which gave the data shown in the flowchart.[6,7]

The anti-PAF activity of **3** was measured by the standard method[2] and was found to be 0% at 2 μM, 10% at 20 μM, and 24% at 200 μM.[8] It is clear from these data that **3** is approximately three orders of magnitude less active than the *tert*-butyl substituted analog **2**. Thus, the *tert*-butyl group of ginkgolide B and various active analogs[2] is essential for anti-PAF potency. It is also interesting that analog **3** exhibits strong antiprotease activity, as does **1**; for this activity the *tert*-butyl group is not crucial.[9]




48.8% HF
(8% in CH3CN)
0°C to 5°C, 6 h
quant.
(COCl)2 (3.0 eq)
DMSO (6.0 eq)
CH2Cl2, -60°C
20 min; Et3N, 83%
CH3P+Ph3Br- (2.5 eq)
t-C5H11O-Na+ (2.0 eq)
C6H6, 10°C, 10 min
70%
Zn (excess)
NH4Cl, MeOH
rt, 8 h, 96%
KHMDS (1.5 eq), THF;
(1.5 eq)
-40°C, 1 h, 65%
KHMDS (2.0 eq), THF
-50°C to 0°C, 1.5 h;
BrCH2CO2t Bu (2.0 eq)
rt, 36 h, 95%
CF3CO2H (5.0 eq)
CH2Cl2, 30°C, 5 h, 86%
TsCl (3.0 eq)
Et3N (6.0 eq)
C6H6, 80°C
3 h, 76%
25% Peracetic acid in EtOAc
-50°C, 16 h, 81%
mCPBA (4.0 eq), CHCl3
pH = 8.0, Phosphate buffer
rt, 40 h, 77%
BCl3 (3.0 eq), CH2Cl2
PhCH2N+Et3Cl- (4.0 eq)
-45°C to 23°C, 5 h, 70%
KHMDS (3.0 eq)
THF,-78°C, 30 min;
(2.0 eq) /
THF, 30 min;
TMSCl (10.0 eq);
1N HCl, 64%
13
14
15
16
17
18
19
20
21
22
23
24
3
Rf = 0.23 (1:3 E/H)
[α]D23 = -155.1°
(c = 1.3, MeOH)
Rf = 0.33 (1:1 E/H)
[α]D23 = -239.3°
(c = 3.0, MeOH)
Rf = 0.57 (3:2 E/H)
[α]D23 = -188°
(c = 0.7, MeOH)
Rf = 0.57 (3:2 E/H)
[α]D23 = -192.5°
(c = 1.2, MeOH)
Rf = 0.66 (EtOAc)
Rf = 0.6 (2:3 E/H)
[α]D23 = -181.4°
(c = 0.9, MeOH)
Rf = 0.38 (1:1 E/MeOH)
[α]D23 = -192.1°
(c = 0.3, MeOH)
Rf = 0.3 (1:1 E/H)
[α]D23 = -52°
(c = 0.1, MeOH)
Rf = 0.15 (1:1 E/H)
[α]D23 = -88.4°
(c = 0.4, MeOH), ee = >96%
Rf = 0.34 (EtOAc)
Rf = 0.55 (EtOAc)
Rf = 0.42 (EtOAc)
[α]D23 = -134°
(c = 0.2, MeOH)
nOe between H1 & H10 = 22%
nOe between H1 & H2 = 0%
nOe between H10 & H12 = 0%
HMDS, (Me3Si)2N
mCPBA, m-ClC6H4CO3H

REFERENCES AND NOTES

1. Braquet, P. *Drugs of the Future* **1987**, *12*, 643-99.
2. Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1989**, *30*, 6959-62.
3. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-3. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-6. (c) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201-4.
4. Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111-33.
5. Satisfactory 500 MHz ^{1}H NMR, infrared and mass spectral data were obtained for each intermediate using chromatographically purified and homogeneous (by tlc analysis) samples.
6. ^{1}H NMR data for intermediates **10**, **12**, and **13** are as follows:
   For **10**: ^{1} H NMR (500 MHz, $CDCl_3$) δ 6.1 (d, 1H, *J* = 11.6 Hz), 5.8 (br s, 1H), 5.62-5.52 (m, 1H), 4.92-4.85 (m, 1H), 4.3 (dd, 1H, *J* = 8.0, 6.0 Hz), 3.8 (s, 3H), 3.1-2.8 (m, 2H), 2.6-2.45 (m, 1H), 2.35-2.2 (m, 1H), 1.8-1.7 (m, 1H), 1.2-0.9 (m, 21H); For **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.1 (m, 1H), 5.82 (m, 1H), 4.5 (m, 1H), 3.3 (dt, 1H, *J* = 19.0, 2.5 Hz), 3.28 (d, 1H, *J* = 9.0 Hz), 2.98 (dt, 1H, *J* = 19.3, 2.0 Hz), 2.2-2.1(m, 1H), 2.05-1.9 (m, 3H), 1.2-1.0 (m, 21H); For **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dt, 1H, *J* = 6.1, 2.1 Hz), 5.67 (dt, 1H, *J* = 6.1, 2.1 Hz), 4.65 (dd, 1H, *J* = 6.6, 3.1 Hz), 4.62 (t, 1H, *J* = 3.3 Hz), 3.28 (dt, 1H, *J* = 18.4, 2.1 Hz), 3.01 (dt, 1H, *J* =18.4, 2.1 Hz), 2.35-2.25 (m, 1H), 2.2-2.1 (m, 1H), 1.9-1.8 (m, 2H), 1.1-0.9 (m, 21H).
7. ^{1}H NMR data for intermediates **19**, **21** - **24** , and **3** are as follows:
   For **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dt, 1H, *J* = 5.9, 2.2 Hz), 5.5 (dt, 1H, *J* = 5.9, 2.1 Hz), 5.16 (t, 1H, *J* = 1.8 Hz), 4.86 (t, 1H, *J* = 2.1 Hz), 4.7 (dd, 1H, *J* = 7.2, 6.0 Hz), 4.25 (d, 1H, *J* = 16.3 Hz), 4.13 (d, 1H, *J* = 16.3 Hz), 2.91 (dt, 1H, *J* = 16.7, 2.2 Hz), 2.88-2.78 (m, 1H), 2.63 (dt, 1H, *J* = 16.7, 2.1 Hz), 2.45-2.35 (m, 1H), 2.25-2.1 (m, 2H); For **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dt, 1H, *J* = 5.9, 2.2 Hz), 5.6 (dt, 1H, *J* = 5.9, 2.4 Hz), 5.1 (t, 1H, *J* = 1.6 Hz), 4.8 (t, 1H, *J* = 7.2Hz), 3.0 (dt, 1H, *J* = 18.9, 2.2 Hz), 2.7 (dt, 1H, *J* = 18.9, 2.4 Hz), 2.98-2.93 (m, 2H), 2.59-2.49 (m, 1H), 2.35-2.29 (m, 1H), 2.22-2.1 (m, 1H), 1.97-1.87 (m, 1H); For **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H), 5.9 (dt, 1H, *J* = 5.8, 2.2 Hz), 5.7 (dt, 1H, *J* = 5.8, 2.2 Hz), 4.72 (m, 1H), 3.07 (dt, 1H, *J* = 19.2, 2.3 Hz), 3.0 (dt, 1H, *J* = 19.2, 2.3 Hz), 2.85 (d, 1H, *J* = 17.7 Hz), 2.6 (d, 1H, *J* = 17.7 Hz), 2.25-2.2 (m, 4H); For **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.15 (t, 1H, *J* = 5.9 Hz), 3.79 (t, 1H, *J* = 1.9 Hz), 3.6 (d, 1H, *J* = 2.2 Hz), 3.0 (d, 1H, *J* = 18.2 Hz), 2.87 (d, 1H, *J* = 15.8 Hz), 2.73 (d, 1H, *J* = 18.2 Hz), 2.4- 2.25 (m, 3H), 2.15-2.0 (m, 1H), 2.0-1.9 (m, 1H); For **24**: ^{1}H NMR (500 MHz, DMSO d_6) δ 6.51 (d, 1H, *J* = 5.8 Hz), 6.2 (s, 1H), 5.12 (d, 1H, *J* = 4.0 Hz), 4.4-4.3 (m, 1H), 3.8 (dd, 1H, *J* = 9.3, 5.8 Hz), 3.0 (s, 2H), 2.74 (dd, 1H, *J* = 13.4, 6.9 Hz), 2.12-2.05 (m, 2H), 2.0-1.7 (m, 3H); For **3**: ^{1}H NMR (500 MHz, DMSO d_6) δ 6.94 (d, 1H, *J* = 6.7 Hz), 6.62 (d, 1H, *J* = 5.8 Hz), 6.1 (s, 1H), 5.17 (d, 1H, *J* = 3.6 Hz), 4.4-4.3 (m, 2H), 3.77 (dd, 1H, *J* = 5.8, 9.2 Hz), 2.41 (dd, 1H, *J* = 13.5, 6.8 Hz), 2.0 (m, 1H), 2.0 -1.6 (m, 4H).

8. We are indebted to Dr. Pierre Braquet and his colleagues for these measurements.
9. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

(Received in USA 15 May 1991)