Tetrahedron Letters, Vol. 34, No. 2, pp. 349-352, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

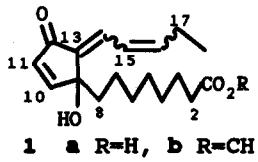
Natural Products Synthesis by Retro Diels–Alder Reaction III[1] Total Synthesis of (±)–Chromomoric Acid D I Methyl Ester[2]

Zhi-Yu LIU* and Xin-Jie CHU

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Abstract: Chromomoric acid D I Methyl ester (D **Ib**) has been synthesized via a retro Diels-Alder reaction as a key step, suggesting structural revision of originally postulated D **Ib** to D **IVb**.

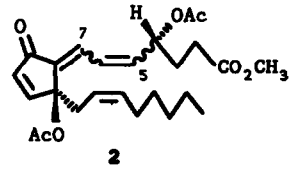
Chromomoric acids D I-IV(**1a**), isolated from *chromolaena morii*[2b], are metabolites of linolenic acid. Their chemical structures are similar to the marine prostanoids clavulones I-III(**2**)[3] which have remarkable biological activities. As these compounds are present only in minute amounts and their stereochemistry is still a matter to be elucidated, the synthesis of this kind of compounds is of current interest to study their biological activity and to determine their absolute configuration. Herein we wish to report a first total synthesis of (±)-chromomoric acid D I methyl ester(D **Ib**).



1 **a** R=H, **b** R=CH_3

Chromomoric acid D I-IV[2b]

I	13E, 15Z
II	13E, 15E
III	13Z, 15E
IV	13Z, 15Z

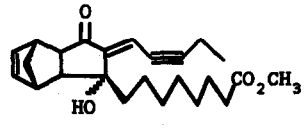


2

Clavulone I-III[3]

I	5Z, 7E
II	5E, 7E
III	5E, 7Z

3

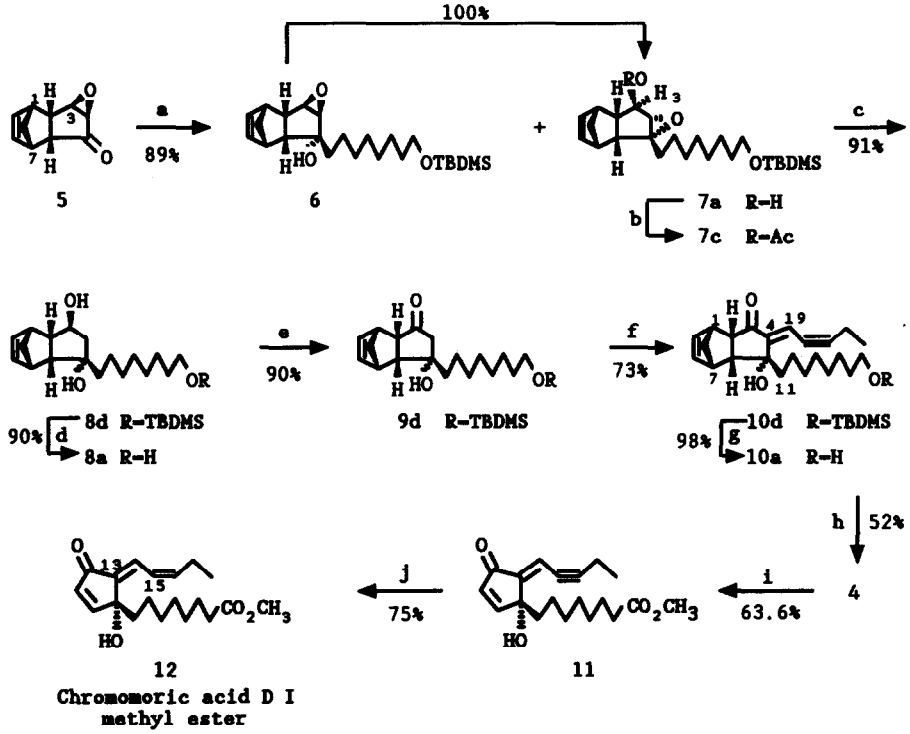


4

The general approach for the synthesis of **2** using a three-component coupling process has been achieved[4]. Our strategy is using a rigid mole-

cule 3 as a starting material for the highly stereoselective preparation of the tertiary alcohol and a retro Diels-Alder reaction as a key step to produce the target molecule.

Treatment of epoxide 5[5],prepared by epoxidation of 3, with a lithium reagent at 0°C for 3h produced stereoselectively a 1:3 mixture of 6 and 7a . When this reaction mixture was stirred overnight at RT, 6 was completely rearranged to 7a and only 7a was isolated. Acetylation of 7a made the δ of H_3 shifted from 3.77 (d) in 7a to 4.42 (d) in 7c indicating that 7a was a secondary alcohol. Regiospecific reduction of 7a gave 8d which was converted into triol 8a. Since compound 4 contains a carbonyl and a carboxyl group, attempts to oxidize triol 8a to a keto acid or a keto aldehyde have been made, but always led to complicated results. However,



Reagents and Conditions: a) $Li(CH_2)_8OTBDMS$ (1.1 equiv.), Et_2O, 0°C, 3h, then rt, 15h; b) Ac_2O, Py, rt, overnight, 93%; c) $LiAlH_4$, THF, 0°C--5°C, 5h; d) $n\text{-}Bu_4N^+F^-$, THF, 30°C, 6h; e) PDC, CH_2Cl_2, 4Å molecular sieve, rt, 2.5 h; f) LDA (2.5 equiv.), EtC≡CCHO (2 equiv.), THF, -78°C, 5min; then -10°--0°C, 4h; rt, 2h; g) HOAc-H_2O-THF(6:3:1), rt, 3h; h) PDC, DMF, 4Å molecular sieve, 5h; then CH_2N_2, Et_2O, 0°C; i) 240°C, 70 mmHg, 5 min; then 2 mmHg, 5 min ; j) H_2, Lindlar Cat. , toluene, 20 min.

oxidation of **8d** afforded **9d** in high yield. Aldol condensation of **9d** with 2-pentynal gave stereo- and chemoselectively **10d**, the newly formed olefinic bond at C-4 was assigned to be *E* configuration in the following context. Conversion of alcohol **10d** to ester **4**[6] was accomplished by cleavage of the silyl ether, oxidation of the resulted alcohol and esterification. Thermolysis of **4**, by heating it in a tube under N_2 and collecting the thermolysis product with a cold finger (cooled with dry ice-acetone) at 240°C (70 mmHg), afforded **11**[7] in 63.6% yield. Hydrogenation of **11** with 5% wt Lindlar Pd-$CaCO_3$ catalyst produced target molecule, chromomoric acid D I methyl ester(**12**)[8].

The stereochemistry of the two olefinic bonds at C-13 and C-15 in **12** were elucidated by analysis of the ^{1}H NMR spectrum of **12**[8] and in comparison with that of natural chromomoric acid D methyl ester reported by Bohlmann[2b]. The *Z* configuration of the olefinic bond at C-15 was shown by the coupling constant ($J_{15,16}$=10.8 Hz) between H-15 and H-16. The configuration of the olefinic bond at C-13 was determined from the δ of H-14. Due to the anisotropy effect of the C-12 carbonyl, the H-14 signal in 13*E* configuration should be observed at lower field than that of 13*Z* isomer[3]. The H-14 signal of our synthetic **12** was at 7.29 ppm and that of natural chromomoric acid D methyl ester reported by Bohlmann was at 6.89 ppm. Therefore **12** is assigned to be D **Ib** having a 13*E* configuration, and the natural one should be D **IVb** having a 13*Z* configuration.

Thus, an efficiently stereo-, regio- and chemoselective synthesis of (±)-chromomoric acid D I methyl ester(D **Ib**) has been achieved. Syntheses of other chromomoric acid D and the optically active ones are in progress.

Acknowledgement We are grateful to Professor F. Bohlmann for sending us the ^{1}H NMR spectra of some of the chromomoric acid methyl esters. Thanks are also due to Mr. Ming Ye for measurement of the 600 MHz ^{1}H NMR spectra.

REFERENCES AND NOTES

1. For part I and II see Liu,Z.-Y.; Shi,W.; Zhang,L. *Synthesis*, 1990, 235, and Zhang,L.; Yang,J.-Y.; Liu,Z.-Y. *Chinese Chemical Letters*, accepted for publication, 1992.
2. F.Bohlmann and his co-workers isolated a group of metabolits of linolenic acid, which all contain a cyclopentenone and named the first isolated compound **chromomoric acid**[2a]. In discussion with Professor F.Bohlmann, we name all of these compounds **chromomoric acid** plus a letter in the alphabetical order:
   2a. Bohlmann,F.; Gupta,R.K.; King,R.M.; Robison,H. *Phytochemistry*, 1981, **20**, 1417.
   2b. Bohlmann,F.; Borthakur,N.; King,R.M.; Robison,H. *Phytochemistry*, 1982, **21**, 125.
   2c. Bohlmann,F.; Singh,P.; Jakupovic,J.; King,R.M.; Robison,H. *Phytochemistry*, 1982, **21**, 371.

Chromomoric acid A[2a]

Chromomoric acid B[2b]

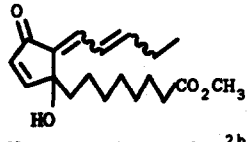
Chromomoric acid C

I 13E,15Z[2c]

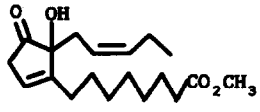
II 13E,15E[2b]

III 13Z,15E[2c]

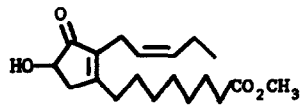
IV 13Z,15Z[2b]



Chromomoric acid D[2b]



Chromomoric acid E[2b]



Chromomoric acid F[2c]

3. (a). Kikuchi,H.; Tsukitani,Y.; Igucji,K.; Yamada,Y.*Tetrahedron Lett.* 1982, **23**, 5171. (b). Baker,B.J.; Okuda,R.K.; Yu,P.T.K.; Scheuer,P.T. *J. Amer. Chem. Soc.*, 1985, **107**, 2976.
4. H.Nagaoka, T.Miyakoshi, Y.Yamada, *Tetrahedron Lett.*, 1984, **25**, 3621.
5. O.L.Chapman and T.C.Hess, *J. Org. Chem.*, 1979, **44**, 962.
6. **4**, IR (neat): 3450, 2200, 1740, 1700, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.15(t, 1H, J=2.4 Hz), 6.08(m, 1H), 5.80(m,1H), 3.59(s, 3H), 3.15(m, 2H), 2.93(m, 1H), 2.75(m, 1H), 2.37(dq, 2H, J=7.0, 2.4 Hz), 2.22(t, 2H, J=7.2 Hz), 1.18-1.78 (m, 14H), 1.16 (s, 1H), 1.08(t, 3H, J=7 Hz); MS (m/z): 84 (M^+), 318 ($M^+-C_5H_6$), 287 ($M^+-C_5H_6-OCH_3$), 286 ($M^+-C_5H_6-CH_3OH$), 161 [$M^+-C_5H_6-(CH_2)_7CO_2CH_3$] ; HRMS: Found 384.2252, calcd.for $C_{24}H_{32}O_4$ 384.2298 .
7. **11**, IR (neat): 3400, 2200, 1740, 1700 1630 cm^{-1}; ^1H NMR (200 HMz, $CDCl_3$): δ 7.31(d, 1H, J=6 Hz), 6.39(t, 1H, J=2.2 Hz), 6.32(d, 1H, J=6Hz), 3.59(s, 3H), 2.42(qd, 2H, J=7.0, 2.2 Hz), 2.23(t, 2H, J=7.0 Hz), 1.05-1.66(m, 16H); MS (m/z): 318 (M^+), 301 (M^+-H_2O+1), 286 (M^+-CH_3OH), 161 [$M^+-(CH_2)_7CO_2CH_3$].
8. **12**, IR (neat): 3400, 3040, 1740, 1700, 1635 cm^{-1}; ^1H NMR(600 MHz, in $CDCl_3$): δ 7.31(dd, 1H, H-10, J=6.0, 0.8 Hz), 7.29(dm, 1H, H-14 J=12.4 Hz), 6.65(ddt, 1H, H-15, J=12.4, 10.8, 1.5 Hz), 6.36(d, 1H, H-11, J=6.0 Hz), 6.08(dtd, 1H, H-16, J=10.8, 7.7, 1.0 Hz), 3.66(s, 3H, CH_3O), 2.39(m, 2H, H-17), 2.28(t, 2H, J=7.6 Hz), 1.98(m, 2H), 1.59 (t, 2H, J=7.0 Hz), 1.23-1.32 (m, 9H), 1.06 (t, 3H, J=7.6 Hz); ^1H NMR (600Hz, in CD_3COCD_3): δ 7.44 (dd, 1H, H-10, J=6.0, 0.8 Hz), 7.14 (ddd , 1H, H-14, J=12.4, 1.1, 0.8 Hz), 6.75 (ddt, 1H, H-15, J= 12.4, 10.8, 1.5 Hz), 6.29 (d, 1H, H-11, J=6.0 Hz), 6.03 (dtd, 1H, H-16, J= 10.8, 7.7, 1.1 Hz), 3.61(s, 3H, CH_3O), 2.37(m, 2H, H-17), 2.27 (t, 2H, H-2, J=7.5 Hz), 1.96 (m, 2H), 1.55 (t, 2H, J=7.3 Hz), 1.22-1.32(m, 9H), 1.05(t, 3H, J=7.6 Hz); MS (m/z): 320 (M^+), 302 (M^+-H_2O), 291 (M^+-Et), 289 (M^+-CH_3O), 288 (M^+-HOCH_3), 273 (M^+-H_2O-Et), 259 (M^+-Et-$HOCH_3$), 163 [$M^+-(CH_2)_7CO_2CH_3$], 55 ($C_4H_7^+$); HRMS: Found 320.2008, Calcd for $C_{19}H_{28}O_4$ 320.1987; UV: λ_{1max}(EtOH) 236nm, ε_{1max}1.83x10^4; λ_{2max}(EtOH) 302nm, ε_{2max}1.20x10^4.

(Received in China 20 October 1992)