Facile Retro Diels–Alder Reaction of a Pentamethyltricyclo[5.2.1.$0^{2,6}$]decenone Derivative: Synthesis of (+)-15(*S*)-Prostaglandin A_2

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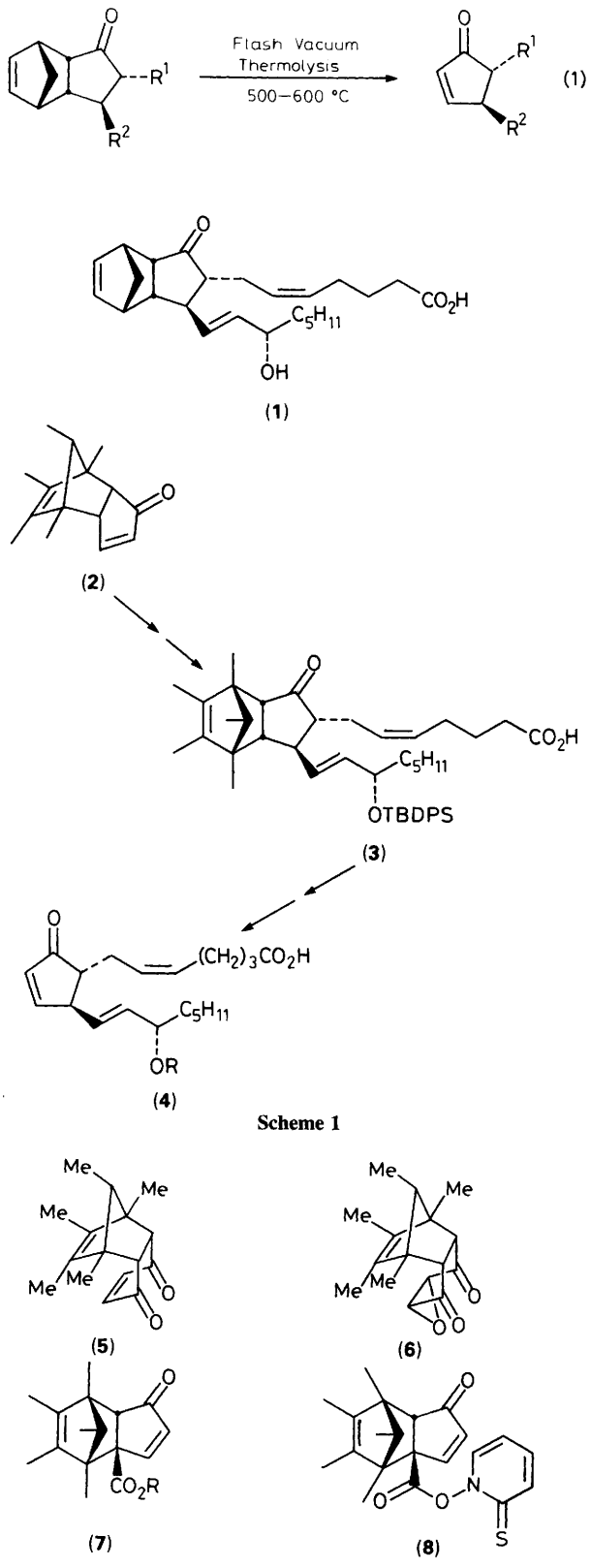
The incorporation of methyl groups into the C(1), C(7), C(8), C(9), and C(10) positions of tricyclo[5.2.1.$0^{2,6}$]decenone (**1**) dramatically accelerates the retro Diels–Alder reaction of (**3**) under Lewis acid catalysis thus permitting access to synthetic natural prostaglandin A_2; the *X*-ray crystal structure of the ammonium salt of (**7**) is reported.

In general, retro Diels–Alder reactions of the type illustrated in equation (1) are routinely conducted under flash vacuum pyrolysis at temperatures in the range of 500—600 °C.[1,2] However [4 + 2] cycloreversion of highly functionalized tricyclo[5.2.1.$0^{2,6}$]decenones of type (**1**) are not compatible with high temperatures or Lewis acid catalysis due to double bond isomerization/rearrangement and/or extensive decomposition. We report that [4 + 2] cycloreversions of the type illustrated in equation (1) can be accelerated by employing the corresponding pentamethyltricyclodecenones [*cf.* compound (**3**)].[3] In addition, we detail a total synthesis of (+)-15(*S*)-prostaglandin A_2 (**4**) (R = H)[4] which features the preparation of enantiomerically pure pentamethyltricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (**2**), the transformation of (**2**) into the functionalized intermediate (**3**) *via* a three component coupling process, and subsequent extrusion of pentamethylcyclopentadiene with formation of cyclopentenone (**4**) (Scheme 1).

The preparation of (+)-(**2**) commences with the known pentamethyl derivative (**5**).[5] Epoxidation (30% H_2O_2, Na_2CO_3, acetone, 0 °C, 1.5 h) of (**5**) provided the crystalline



Scheme 1

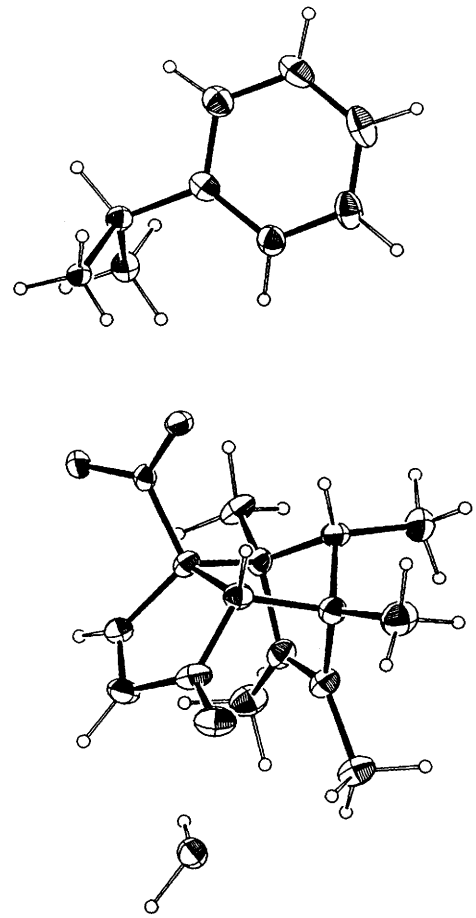
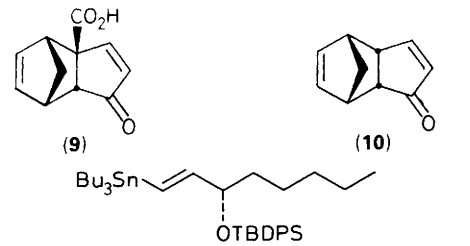


Figure 1. ORTEP drawing of the (*R*)-(−)-α-methylbenzylamine salt of carboxylic acid (**7**) (R = H).

epoxide (**6**), m.p. 88.5—89.5 °C, which was subjected to a Favorskii-type ring contraction.[6] Exposure of (**6**) to 1.0 equiv. of sodium methoxide in methanol (45 °C, 1.5 h) gave rise to ester (**7**) (R = Me) in 74% yield. Hydrolysis (10% KOH/MeOH, 50 °C, 17 h) of (**7**) (R = Me) provided the corresponding acid (**7**) (R = H) in 92% yield. The racemic acid (**7**) (R = H) readily formed a crystalline salt with *R*-(−)-α-methylbenzylamine. Recrystallization of the salt from wet ethyl acetate followed by acidification afforded resolved carboxylic acid (**7**) (R = H), $[\alpha]_D^{23}$ +137.0° (*c* 6.4, $CHCl_3$). The absolute configuration of (**7**) was unambiguously established by single-crystal *X*-ray analysis† of the crystalline ammonium salt (Figure 1), $[\alpha]_D^{23}$ +51.5° (*c* 10.8, $CHCl_3$). Decarboxylation of (**7**) (R = H) was realized employing the radical decarboxylation procedure of Barton.[7] Conversion (oxalyl chloride, $CHCl_3$) of (**7**) (R = H) into the corresponding acid chloride followed by treatment with *N*-hydroxypyridine-2-thione afforded the *N*-acyloxypyridine-2-thione (**8**) which was exposed to t-butyl mercaptan in benzene at 60 °C containing 4-dimethylaminopyridine. Enantiomerically pure (**2**), $[\alpha]_D^{23}$ +216° (*c* 6.4, $CHCl_3$), was obtained in 70% overall yield. Attempts to thermally decarboxylate (+)-(**7**) (R = H) in dimethylform-

† *Crystal data*: $[C_{16}H_{19}O_3^-][C_8H_{12}N^+]\cdot H_2O$, *M* = 399.53, orthorhombic, space group $P2_12_12_1$, *a* = 88.799(2), *b* = 22.299(7), *c* = 11.604(2) Å, *U* = 2276.7 Å^3, D_c = 1.166 g cm^{-3}, *Z* = 4, Mo-K_α radiation, 3205 data collected, 1732 unique, $6 < 2\theta < 45°$, *R* = 0.0436, R_w = 0.0422. The structure was solved by a combination of direct methods (MULTAN) and Fourier techniques. All hydrogen atoms were clearly visible in a difference Fourier synthesis phased on the non-hydrogen parameters. All hydrogen atoms were refined isotropically and non-hydrogen atoms anisotropically in the final cycles. As shown in Figure 1, there is a water of crystallization present in the crystal. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

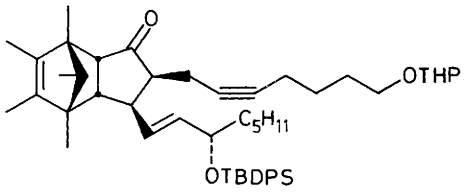


(9) (10)

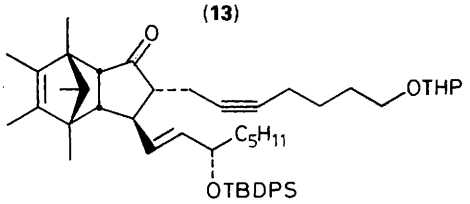
(11)

$ICH_2C \equiv CCH_2CH_2CH_2CH_2OTHP$

(12)



(13)



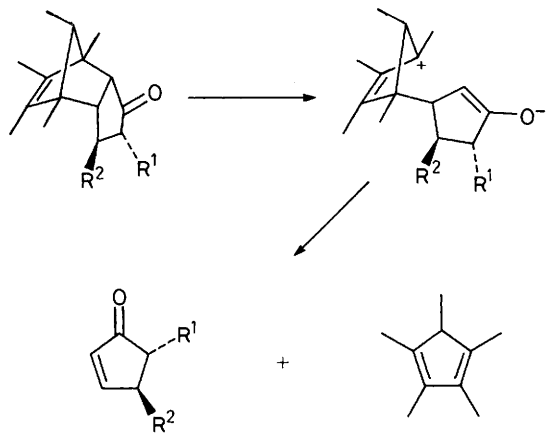
(14)

(THP = tetrahydropyran-2-yl)

amide (150 °C) lead to the formation of (**2**), however the material obtained was essentially racemic. Interestingly, the normethyl analogue (+)-(**9**) undergoes smooth decarboxylation at *ca.* 150 °C in dimethylformamide leading to (−)-(**10**).[8]

A three-component coupling process[9] was employed to elaborate (**3**). A solution of (+)-tricyclo[5.2.1.$0^{2,6}$]decadienone (**2**) in tetrahydrofuran (THF) was added to a cooled (−78 °C) solution of the mixed cyanocuprate reagent prepared [THF, BuLi (2.4 equiv.), −78 °C, 1 h; CuCN (1.2 equiv.), −78 °C, 1 h] from the vinylstannane (**11**). After 30 min, hexamethylphosphoramide (10 equiv., 15 min, −78 °C), tributyltin chloride (1.0 equiv., 10 min, −78 °C to 40 °C), and propargylic iodide (**12**) (5.0 equiv., −40 °C to room temp., 1.25 h) were added sequentially, giving rise to intermediate (**13**). Exposure of (**13**) to 5% methanolic lithium hydroxide–THF (3 : 1) at 55 °C for 10 h afforded in 82% overall yield from (+)-(**2**), tricyclodecenone (**14**). Compound (**14**) was smoothly transformed *via* a three-step sequence [(i) HOAc : THF : H_2O (3 : 1 : 1), 50 °C, 36 h; (ii) H_2, 5% Pd/$CaCO_3$(Pb), MeOH : benzene (1 : 1), 1.5 h; (iii) Jones reagent, acetone, 0 °C, 45 min] into the key intermediate (**3**), $[\alpha]_D^{23}$ −24° (*c* 5.8, $CHCl_3$), in 93% overall yield.

Having secured enantiomerically pure tricyclodecenone (**3**), it was subjected to [4 + 2] cycloreversion. Exposure of a 0.06 M solution of (**3**) in 1,2-dichloroethane containing 3.5 equiv. of dimethylaluminium chloride and 5.0 equiv. of fumaronitrile cooled to 10 °C over 48 h gave rise to a 70% yield of (**4**) (R = t-butyldiphenylsilyl), $[\alpha]_D^{23}$ +57.0° (*c* 5.6, $CHCl_3$). Cleavage (50% HF/pyridine/THF (1 : 2 : 17), 45 °C, 12 h) of the t-butyldiphenylsilyl ether provided in 86% yield prostaglandin A_2 (**4**), (R = H), $[\alpha]_D^{23}$ + 129.0° (*c* 7.6, $CHCl_3$) [lit.[4c] $[\alpha]_D^{23}$ +130° (*c* 1.26, $CHCl_3$)]. The structure of the synthetic natural PGA_2 was confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopy, and TLC analysis.



Scheme 2

Attempts to employ Lewis acids to effect a retro Diels–Alder reaction on the nor-methyl system (**1**) have met with no success. The major problem encountered is the instability of the protected allylic alcohol unit on the omega side chain. The observed rate acceleration in the case of substrate (**3**) is due to a combination of steric and electronic effects. However the major contributor to lowering of the activation energy is undoubtedly the presence of the C(1) methyl group which gives rise *via* a non-concerted process to a polarized transition state, (Scheme 2). The ability to accelerate the retro Diels–Alder process by incorporating methyl groups into the 1, 7, 8, 9, and 10 positions of a tricyclo [5.2.1.$0^{2,6}$]decenone should find useful applications in organic synthesis.[10]

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References

1 G. Stork, J. G. Nelson, F. Rouessac, and O. Gringore, *J. Am. Chem. Soc.*, 1971, **93**, 3091.
2 For reviews on retro Diels–Alder reactions see: J.-L. Ripoll, A. Rouessac, and F. Rouessac, *Tetrahedron*, 1978, **34**, 19; M.-C. Lasne and J.-L. Ripoll, *Synthesis*, 1985, 121; A. Ichihara, *ibid.*, 1987, 207.
3 For trimethylsilyl accelerated retro Diels–Alder reactions see: P. Magnus, P. M. Cairns, and J. Moursounidis, *J. Am. Chem. Soc.*, 1987, **109**, 2469.
4 For previous syntheses of (+)-15(*S*)-PGA_2 see: (a) E. J. Corey and G. Moinet, *J. Am. Chem. Soc.*, 1973, **95**, 6831; (b) E. J. Corey and J. Mann, *ibid.*, 1973, **95**, 6833; (c) G. Stork and S. Raucher, *ibid.*, 1976, **98**, 1583; (d) R. F. Newton, D. P. Reynolds, J. Davies, P. B. Kay, S. M. Roberts, and T. W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1983, 683.
5 D. J. Burnell and Z. Valenta, *J. Chem. Soc., Chem. Commun.*, 1985, 1247.
6 W. Herz, V. S. Iyer, and M. G. Nair, *J. Org. Chem.*, 1975, **40**, 3519.
7 D. H. R. Barton, D. Crich, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1983, 939.
8 A. J. H. Klunder, W. B. Huizinga, P. J. M. Sessink, and B. Zwanenburg, *Tetrahedron Lett.*, 1987, **28**, 357.
9 *Cf.* M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, 1985, **107**, 3348; C. R. Johnson and T. D. Penning, *ibid.*, 1986, **108**, 5655; E. J. Corey, K. Niimura, Y. Kinishi, S. Hashimoto, and Y. Hamada, *Tetrahedron Lett.*, 1986, **27**, 2199.
10 *Cf.* A. P. Marchand, V. Vidyasagar, S. C. Suri, R. D. Thomas, and D. H. Ellington, *J. Org. Chem.*, 1989, **54**, 3751.