Synthesis of (3*S*,4*R*)-Eldanolide and (5*S*,12*R*)-Leukotriene-B_4 through Photolysis of Optically Active Hydroxy-7,7-dimethylbicyclo[3.2.0]heptanones

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Photoisomerisation of 3-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-ones is the key step in a new route to the pheromone eldanolide while leukotriene-B_4 is available through a photolytic retro[2 + 2] reaction of 2-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-ones.

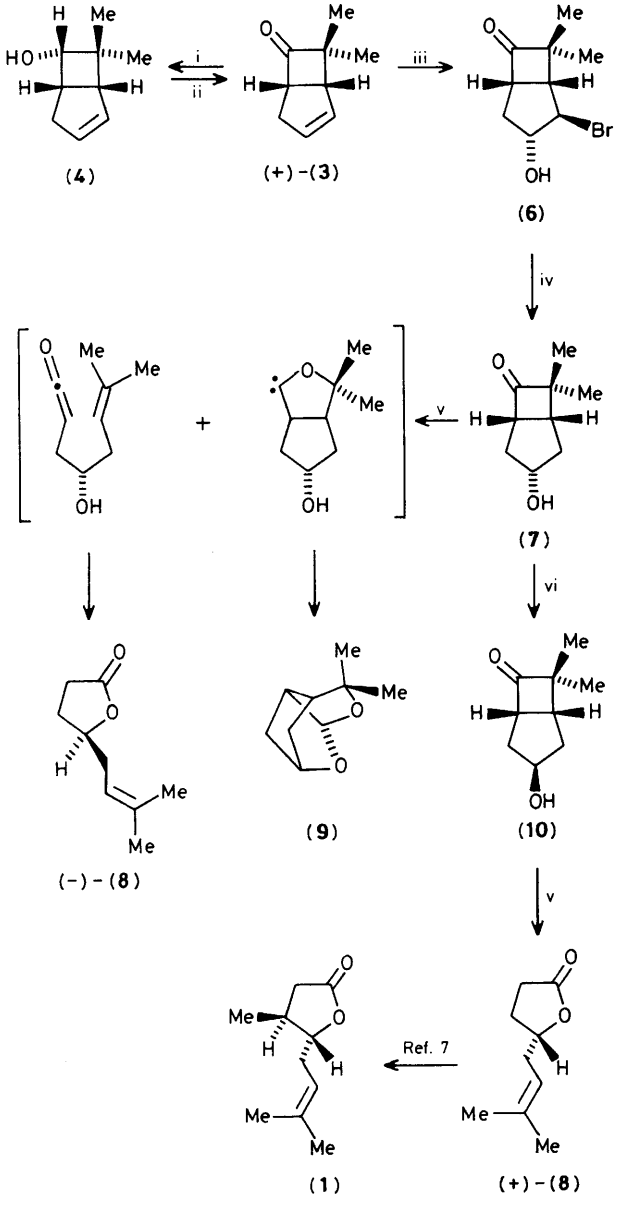
On photolysis, substituted cyclobutanones can undergo three transformations: (a) ring expansion to give an oxacarbene, (b) decarbonylation, or (c) retro[2 + 2] cycloaddition.[1] When the four-membered ring ketone is incorporated into the bicyclo[3.2.0]heptane skeleton only products from breakdown pathways (a) and (c) are observed.[2] The cyclobutanone → oxacarbene pathway is usually favoured,[3] but in the absence of an efficient trap for the oxacarbene, the reversibility of the cyclobutanone/oxacarbene transformation[4] leads to increased formation of product(s) derived from the retro[2 + 2]reaction. In earlier work we showed that a photo-generated ketene could be trapped intramolecularly using a strategically placed epoxide group.[5] We now report that, commencing with suitably functionalised bicycloheptanones, formation and intramolecular trapping of the derived alkenylketene can provide routes to the natural products (+)-eldanolide (**1**) and (+)-leukotriene-B_4 (**2**). The former compound is an attractant pheromone produced by the male African sugar-cane borer *Eldana saccharina* (Wlk), a major pest on sugar cane and maize in many African countries.[6] Interest in this substance is reflected in the number of syntheses of racemic and optically active eldanolide that have been published recently.[7,8] Leukotriene-B_4 (LT-B_4) is an important metabolite of arachidonic acid.[9] It is a powerful chemotactic agent and circumstantial evidence suggests that LT-B_4 may be an important mediator of psoriasis, ulcerative colitis, and dermatitis.[10] A number of synthetic routes to LT-B_4 have been reported.[11]

In order to obtain the target molecules in optically active form in the naturally occurring configuration we needed to separate the enantiomers of the starting material (±)-dimethylbicyclo[3.2.0]hept-2-en-6-one (**3**).[12] Incubation of the ketone (**3**) with the fungus *Mortierella ramanniana* gave nearly equal quantities of two alcohols in *ca.* 50% overall yield.[13] The less polar alcohol ($[\alpha]_D$ −112°) was identical chromatographically to the major product derived by sodium borohydride reduction of the ketone (**3**) and the hydroxy group was consequently assigned as 6-*endo*. The more polar product ($[\alpha]_D$ +109°) co-chromatographed with the racemic

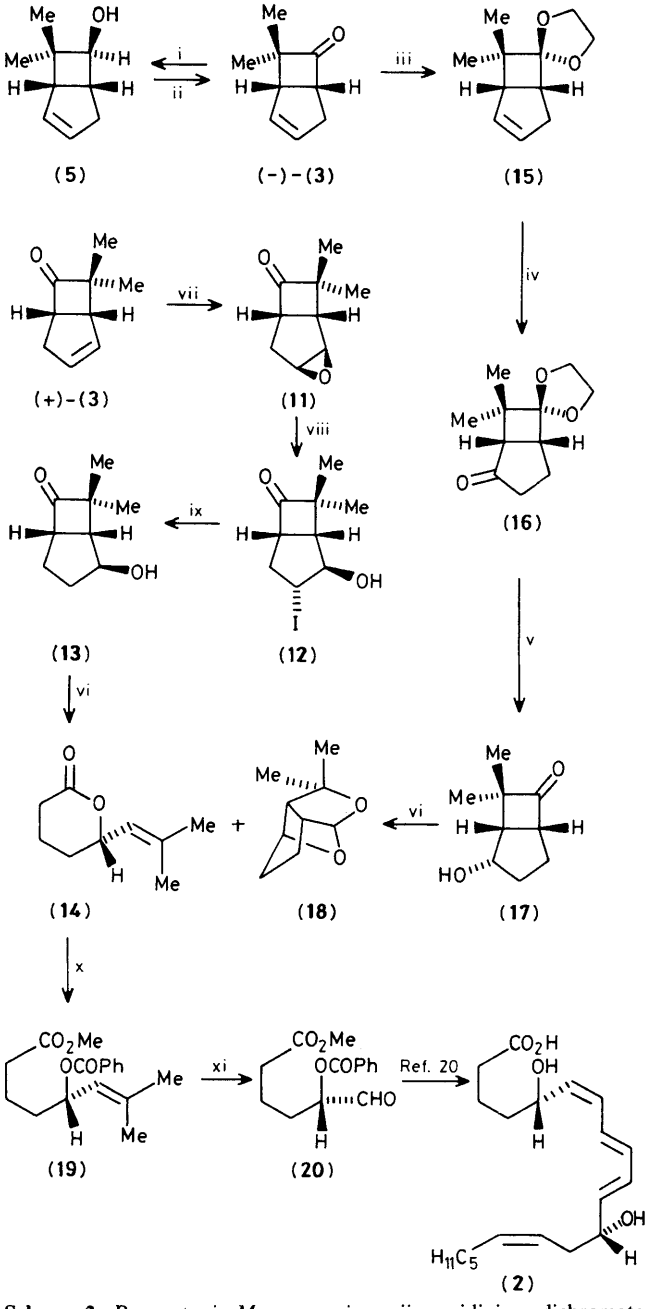
6-*exo*-alcohol. Both the *endo*- (**4**) and the *exo*-alcohol (**5**) were obtained in satisfactory optical purity [80 and >95% enantiomeric excess (e.e.) respectively as judged by g.l.c. over a chiral stationary phase].

The alcohol (**4**) was oxidized using pyridinium dichromate to give (+)-7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (**3**). Treatment of this ketone with *N*-bromoacetamide in aqueous acetone gave the bromohydrin (**6**) in excellent yield (Scheme 1).[14] Hydrodebromination of the bromohydrin (**6**) with tri-n-butyltin hydride gave the hydroxyketone (**7**) which was recrystallised. Photolysis of a solution of ketone (**7**) in pentane using a medium-pressure mercury lamp and quartz apparatus gave the γ-lactone (−)-(**8**) (34%), $[\alpha]_D$ −19°, (through intermediate formation of the alkenylketene[15]) and the acetal (**9**) (30%) (through intramolecular attack of the pendant hydroxy group on the oxacarbene moiety[16]). The hydroxy group in the bicycloheptanone (**7**) was inverted using the Mitsunobu procedure to give the 3-*exo*-hydroxybicycloheptanone (**10**). Photolysis of this compound in pentane gave the lactone (+)-(**8**) (40%), $[\alpha]_D$ +20° (lit.[7] $[\alpha]_D$ +20°) and only a trace of the corresponding acetal. The lactone (+)-(**8**) can be converted into 3*S*,4*R*-eldanolide (**1**) using a three-step procedure.[7]

Dimethylbicycloheptenone (+)-(**3**) was converted into the 2,3-*exo*-epoxide (**11**) using *m*-chloroperoxybenzoic acid (Scheme 2). The steric and electronic influence of the geminal methyl groups militates against the alternative possibility, namely Baeyer–Villiger oxidation. Treatment with aqueous



Scheme 1. *Reagents:* i, *M. ramanniana*; ii, Pyridinium dichromate (70%); iii, MeCONHBr, H_2O, acetone (81%); iv, Bu^n_3SnH, azoisobutyronitrile (AIBN), toluene (82%); v, *hν*, pentane; vi, Ph_3P, diethyl azodicarboxylate (DEAD), $PhCO_2H$, tetrahydrofuran (THF) (78%) then K_2CO_3, MeOH (95%).



Scheme 2. *Reagents:* i, *M. ramanniana*; ii, pyridinium dichromate (70%); iii, $(CH_2OH)_2$, H^+ (80%); iv, B_2H_6 then NaOH, H_2O_2 then pyridinium dichromate (43%); v, $NaBH_4$ then H^+, H_2O (90%); vi, *hν*, pentane; vii, *m*-$ClC_6H_4CO_3H$ (52%); viii, HI, H_2O (94%); ix, Bu^n_3SnH, C_6H_6 (87%); x, Et_3N, MeOH then PhCOCl (85%); xi, O_3 then Me_2S (100%).

hydroiodic acid gave a single iodohydrin (**12**)[17] and hydrodeiodination was effected using tri-n-butyltin hydride to afford the required hydroxyketone (**13**). Photolysis in the usual manner gave the δ-lactone (**14**) $[\alpha]_D$ +7° as the sole non-polar product (40%).

In a second route to the δ-lactone (**14**), the ketone (−)-(**3**) was first protected as the acetal (**15**). Hydroboration of the alkene unit in (**15**) proceeded with very high selectivity to give a single hydroxyacetal (60%) which was oxidised directly to afford the bicycloheptan-2-one (**16**) (71%) as the only identifiable product. Similar unpredicted, highly selective hydroboration reactions of bicycloalkenes have been reported previously.[18] Sodium borohydride reduction and deprotection gave the 2-*endo*-hydroxybicycloheptanone (**17**), a compound prepared recently by Vandewalle by a completely different route.[19] Photolysis of the hydroxyketone (**17**) gave the δ-lactone (**14**) (46%), $[\alpha]_D$ +9° and the strained acetal (**18**) (17%).

Treatment of the lactone (+)-(**14**), $[\alpha]_D$ +9° with triethylamine in methanol followed by benzoylation *in situ* gave the diester (**19**) which on ozonolysis furnished the known aldehyde (**20**), $[\alpha]_D$ −32° (lit.[20] $[\alpha]_D$ −34.4°). The synthesis of naturally occurring optically active LT-B_4 (**2**) can be completed simply by a Wittig reaction, deprotection, and chromatography.[20]

Finally it is noteworthy that, since the ketone (**3**) is prepared by cycloaddition of dimethylketene and cyclopentadiene, these new syntheses of eldanolide and leukotriene-B_4 incorporate a ketene–alkene metathesis.

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References

1 D. R. Morton and N. J. Turro, *Adv. Photochem.*, 1974, **9**, 197.
2 R. F. Newton, D. P. Reynolds, N. M. Crossland, D. R. Kelly, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1583; G. Jones and S. A. Zalk, *Tetrahedron Lett.*, 1973, 4095; H. U. Hostettler, *ibid.*, 1965, 687; for an exceptional case see G. Jones and L. P. McDonnell, *J. Am. Chem. Soc.*, 1976, **98**, 6203.
3 C. C. Howard, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, D. R. Kelly, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1980, 853; J. Davies, S. M. Roberts, D. P. Reynolds, and R. F. Newton, *ibid.*, 1981, 1317.
4 E. Lee-Ruff, A. C. Hopkinson, and H. Kazarians-Moghaddam, *Tetrahedron Lett.*, 1983, **24**, 2062; R. D. Miller, P. Golitz, J. Janssen, and J. Lemmens, *J. Am. Chem. Soc.*, 1984, **106**, 7277.
5 H. G. Davies, S. M. Roberts, B. J. Wakefield, J. A. Winders, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1984, 640; see also L. Rodriquez-Hahn, M. Jimenez, R. Saucedo, M. Soriano Garcia, R. A. Toscano, and E. Diaz, *Tetrahedron*, 1983, **39**, 3909; M. Nitta, A. Omata, and H. Nakatani, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2009.
6 P. R. Atkinson, *J. Entomol. Soc. South Afr.*, 1980, **43**, 171.
7 J. P. Vigneron, R. Meric, M. Larcheveque, A. Debal, J. Y. Lallemand, G. Kunesch, P. Zagatti, and M. Gallois, *Tetrahedron*, 1984, **40**, 3521.
8 T. Uematsu, T. Umemura, and K. Mori, *Agric. Biol. Chem.*, 1983, **47**, 597; Y. Yokoyama and M. Yunokihara, *Chem. Lett.*, 1983, 1245; T. K. Chakraborty and S. Chandrasekaran, *Tetrahedron Lett.*, 1984, **25**, 2891; K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *ibid.*, 1985, **26**, 861.
9 P. J. Piper, *Physiol. Rev.*, 1984, **64**, 744.
10 C. L. Malmsten, *Crit. Revs. Immunol.*, 1984, **4**, 307; A. W. Ford-Hutchinson, *J. Allergy Clin. Immunol.*, 1984, 437; T. Ruzicka, T. Simmet, B. A. Peskar, and O. Braun-Falco, *Lancet*, 1984, 222.
11 Y. Le Merrer, A. Dureault, C. Gravier, D. Languin, and J. C. Depezay, *Tetrahedron Lett.*, 1985, **26**, 319, and references therein.
12 M. Rey, S. M. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **53**, 417.
13 M. Dawson, G. C. Lawrence, S. M. Roberts, M. K. Turner, and W. F. Wall, unpublished results; *cf.* M. J. Dawson, G. C. Lawrence, G. Lilley, M. Todd, D. Noble, S. M. Green, S. M. Roberts, T. W. Wallace, R. F. Newton, M. C. Carter, P. Hallett, J. Paton, D. P. Reynolds, and S. Young, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2119.
14 S. M. Roberts and Z. Grudzinski, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1767.
15 For other examples of intramolecular trapping of photolytically derived ketenes by neighbouring hydroxy groups see G. Quinkert, G. Fischer, U. M. Billhardt, J. Glenneberg, H. Hertz, G. Dünner, E. F. Paulus, and J. W. Bats, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 440; I. Kouno and N. Kawano, *Chem. Pharm. Bull.*, 1983, 4193; S. Stiver and P. Yates, *Tetrahedron Lett.*, 1984, **25**, 3289.
16 *Cf.* D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Am. Chem. Soc.*, 1970, **92**, 4349.
17 J. M. Berge, S. M. Roberts, H. Suschitzky, and J. E. G. Kemp, *J. Chem. Soc., Perkin Trans. 2*, 1980, 690 and references therein.
18 J. Toczek, T. V. Lee, and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1985, 371; S. V. Govindan, T. Hudlicky, and F. J. Koszyk, *J. Org. Chem.*, 1983, **48**, 3581.
19 K. Bruneel, D. De Keukeleire, and M. Vandewalle, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1697.
20 L. S. Mills and P. C. North, *Tetrahedron Lett.*, 1983, **24**, 409.