

Perkin Communications

Stereochemistry of Substituted 1-Alkoxybicyclo[2.2.2]octenes; Diels–Alder synthesis *versus* Tandem-Michael Strategy

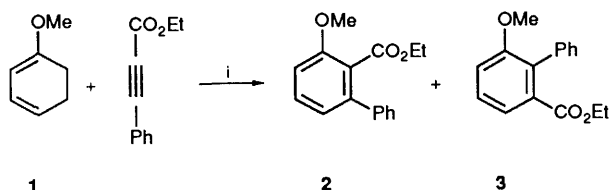
John H. Bateson,* Carol F. Smith and J. Bruce Wilkinson

SmithKline Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey, RH3 7AJ, UK

Diels–Alder reactions of 1-methoxy- and 1-ethoxy-cyclohexa-1,3-dienes with ethyl cinnamate or ethyl 4,4,4-trifluorocrotonate favour the (1*RS*,2*RS*,3*SR*,4*RS*) (*exo*-carboxylate) bicyclo[2.2.2]octene stereochemistry, **5**,**6**,**9**, whereas the bicyclo-octenes derived from 3-alkoxycyclohex-2-enones by Tandem-Michael additions are obtained exclusively as the (1*RS*,2*SR*,3*RS*,4*RS*) (*endo*-carboxylate) isomers **16**.

The preparation of 1-alkoxycyclohexa-1,3-dienes by isomerisation of their accessible 1,4-diene counterparts has been described¹ by Birch, and the regiochemistry of their Diels–Alder additions to acrylates and tetrolates is well documented.^{1–3} However, for additions to enoates, assignments of the relative stereochemistry of the resulting substituted bicyclo[2.2.2]octenes has been less certain. In the course of a spirovetivane synthesis, Murai *et al* observed⁴ a preference for the *endo*-carboxy isomer to be formed in the reaction of methyl acrylate with a substituted methoxy diene. Other applications of 1-methoxybicyclo[2.2.2]octane chemistry include studies by Holmes^{5–8} of the α -chloroacrylonitrile adducts of substituted methoxycyclohexadienes, and their subsequent fragmentation to 4-substituted cyclohexanones.

In our programme of investigation of bridgehead-substituted bicyclo[2.2.2]octenes, we examined the reactions of alkoxyhexadienes with phenylpropiolate and cinnamate esters. Diels–Alder reaction of the diene **1** with ethyl phenylpropiolate (Scheme 1) provided ethyl 2-methoxy-6-phenylbenzoate † **2**



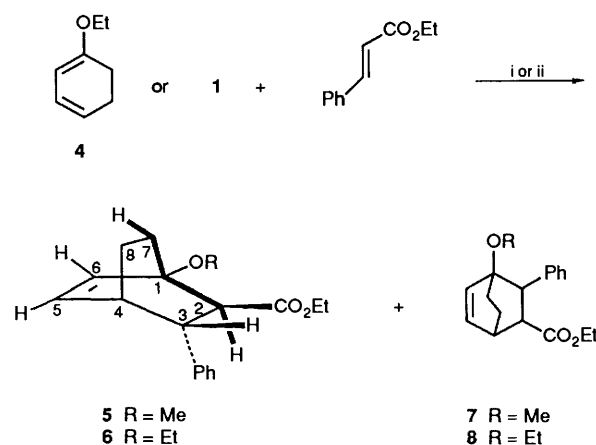
Scheme 1 Conditions: i, neat, 120 °C, 3 d

(43%) and its 3-methoxy-2-phenyl isomer **3** (25%) (7:4 ratio). (The structural assignments were conformed by n.O.e. experiments). These aromatic compounds arise by retro [4 + 2] elimination of ethylene from the intermediate (unisolated) bicyclo[2.2.2]octadienes, and their structures indicate that the carboxylate and methoxy groups are adjacent in the major adduct regioisomer.³

Diels–Alder addition of the methoxy diene **1**‡ to ethyl cinnamate (Scheme 2) was effected by heating in benzene in the presence of dichloromaleic anhydride (DCMA) and *t*-butyl-*p*-cresol (TBC) in a sealed system (QVF apparatus, 100 °C, 21 d). This provided ethyl (1*RS*,2*RS*,3*SR*,4*RS*)-1-methoxy-3-phenylbicyclo[2.2.2]oct-5-ene-2-carboxylate **5** (25%). Two minor products were obtained, and these proved to be the isomers **7**

† All new compounds gave satisfactory spectroscopic and analytical data. The esters **5–16** are racemic; one enantiomer is depicted for convenience.

‡ Commercially available material (Aldrich Chemical Co.) containing ca. 35% of the 1,4-diene. DCMA is an effective isomerisation catalyst.¹

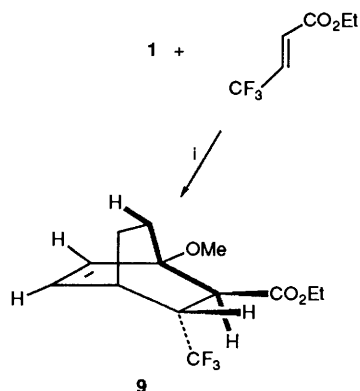


Scheme 2 Conditions: i, PhH, DCMA (0.1 mol %), TBPC (5 mol %), QVF, 100 °C, 21 d; ii, xylene, DCMA (0.1 mol %), TBPC (5 mol %), heat, 5 d

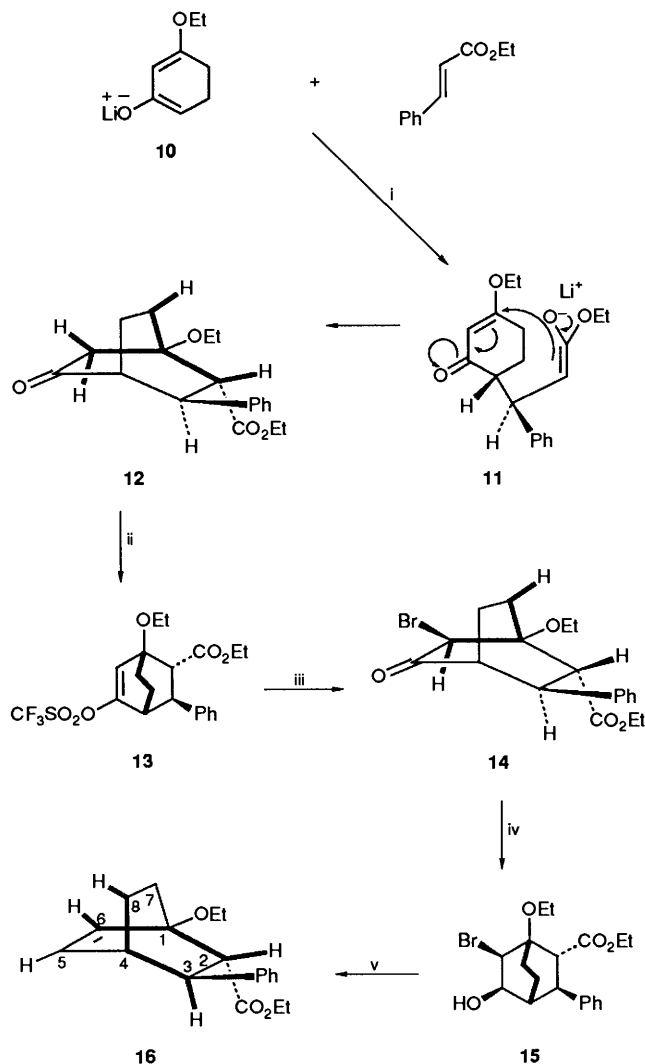
arising from the alternative regiochemical mode of addition. In xylene at reflux, equilibrium was more rapidly established (5 d), but gave lower yields of **5** (14%). Similar results were observed using the ethoxy diene **4**, affording bicyclo[2.2.2]octene **6** (27%). The reaction between the methoxy diene **1** and ethyl 4,4,4-trifluorocrotonate (Scheme 3) was run in refluxing benzene in the presence of DCMA and TBC for 4 d and gave ethyl(1*RS*,2*RS*,3*SR*,4*RS*)-1-methoxy-3-trifluoromethylbicyclo[2.2.2]oct-5-ene-2-carboxylate **9** in excellent yield (96%). The stereochemistry of the adducts **5**, **6** and **9** follows from a detailed analysis of the ¹H NMR spectra.§ The most conclusive evidence comprises the demonstration in each case of a *W*-coupling relationship between the 2-H* and a 7-H (thickened lines).⁴

Tandem-Michael reactions provide an alternative route to bicyclo[2.2.2]octenes.^{9–11} The enolate **10** was obtained (Scheme 4) by the reaction of 3-ethoxycyclohex-2-enone with lithium dicyclohexylamide. This was added to ethyl cinnamate at low temperature. These reactions (proceeding *via* intermediates of type **11**) result in the opposite (*endo* carboxylate)

§ Selected spectral data. (250 MHz) (CDCl₃). Adduct **6**: δ_{H} (*inter alia*) 2.64 (1 H, m, 4-H), 2.91 [1 H, dd, *J* 6.5 and 2 (W-coupling), 2-H], 3.40 (1 H, br d, *J* 6.5, 3-H), 6.27 (1 H, dd, *J* 8.5 and 6, 5-H) and 6.52 (1 H, d, *J* 8.5, 6-H). Adduct **9**: δ_{H} 2.73 [1 H, dd, *J* 7 and 2 (W-coupling), 2-H], 2.79 (1 H, m, 4-H), 2.93 (1 H, quin. d, *J* 7 and 1, 3-H), 6.21 (1 H, dd, *J* 8.5 and 6.5, 5-H) and 6.45 (1 H, d, *J* 8.5, 6-H). W-couplings were identified by double-resonance and COSY-45 experiments.



Scheme 3 Conditions: i, PhH, DCMA (0.1 mol %), TBPC (5 mol %)

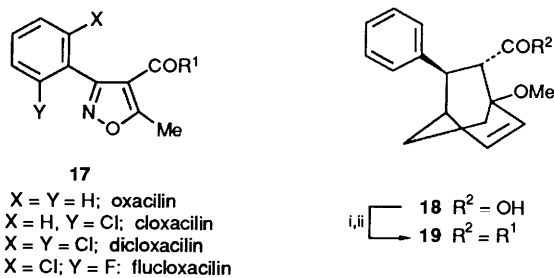


Scheme 4 Reagents: i, THF, -70°C , 1 h; NH₄Cl(aq), 75%; ii, Et₃N, TMSOTf, $0^{\circ}\text{C} \rightarrow$ room temp., 1.5 h; iii, NBS, CH₂Cl₂, 5 min, 86%; iv, NaBH₄, THF-EtOH-H₂O, 82%; v Zn (act.), EtOH, heat, 1 h, 99%

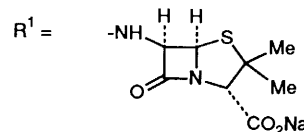
stereochemistry from that observed to predominate in the cycloadditions. The ketone **12** exhibits *W*-coupling between 2-H^β and 6-H^β, and an additional *W*-coupling is evident for 6-H^α and a 7-H signal. Conversion into the bicyclooctene **16** was

* Selected spectral data. Isomer **16**: δ₁₁ 2.53 (1 H, m, 4-H), 2.91 (2 H, m, 2-H and 3-H), 6.30 (1 H, d, *J* 8.5, 6-H) and 6.48 (1 H, dd, *J* 8.5 and 6.5, 5-H).

† *J* Values in Hz throughout.



17
 X = Y = H; oxacillin
 X = H, Y = Cl; cloxacillin
 X = Y = Cl; dicloxacillin
 X = Cl; Y = F; flucloxacillin



Scheme 5 Reagents: i, SOCl₂, Et₃N, CH₂Cl₂, $-20 \rightarrow -10^{\circ}\text{C}$; ii, 6-APA, Et₃N, MIBK-H₂O, $0^{\circ}\text{C} -$ room temp., 2 h.

effected using a modification (Scheme 4) of Schlessinger's procedure;¹² preparation of the trimethylsilyl trifluoromethanesulphonate **13**, followed by electrophilic bromination with *N*-bromosuccinimide provided the bromo ketone **14** (*β*-orientation), in which the *W*-coupling to 2-H^β is absent. Reduction to the bromohydrin **15** with sodium borohydride, followed by reductive elimination with zinc in refluxing ethanol, gave the alkene **16** in excellent yield. This product was different (¹H NMR)* from the isomer **6** (*vide supra*). A 400 MHz ¹H NMR study of **16** involving analysis of the resolution enhanced spectrum, together with the COSY-45 2D spectrum, differentiated the 2-H [long-range coupled to the C-6 olefinic proton (⁴*J*_{2,6} 1)†] from the 3-H signal. The latter is *W*-coupled to an 8-H resonance (*J* 2). This confirms both the stereochemistry of precursor ketone **12** and, by inference, that of the Diels-Alder adduct **6**.

The oxacillins (Scheme 5, **17**) are well known¹³ antibacterial agents, active against Gram-positive bacteria. On steric grounds, we expected that bicyclooctenyl penicillins (*e.g.* **19**) would possess similar properties. Hydrolysis of the ester **5** (KOH, EtOH-H₂O, heat, 3 h) to the carboxylic acid **18**, m.p. 198–202 °C, followed by reaction with the acid chloride of 6-aminopenicillanic acid gave a (1:1) ratio of the penicillin diastereoisomers **19**, (one diastereoisomer depicted). This preparation was active against *Staphylococcus aureus* (*S.a.*) species and was stable to *β*-lactamase. In this series we have shown that in order to confer the latter property, the presence of the bridgehead alkoxy group is essential, and this parallels the importance of the isoxazolyl methyl group of oxacillins **17**. Hoover has prepared¹⁴ bicyclo[2.2.1]heptenyl derivatives corresponding to **19**, but lacking a bridgehead substituent, and these were ineffective against *β*-lactamase producing *S.a.* organisms. Penicillin preparations analogous to esters **6**, **9** and **16** also exhibited the biological properties of **19**. All were absorbed by the oral route in mice; full details will be reported elsewhere.

References

- 1 A. J. Birch and K. P. Dastur, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1650.
- 2 A. J. Birch and J. S. Hill, *J. Chem. Soc. C*, 1966, 419.
- 3 C. K. Kanakam, N. S. Mani, H. Ramanathan and G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1907.
- 4 A. Murai, S. Sato and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2276.
- 5 N. C. Madge and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1980, 956.
- 6 A. B. Holmes and N. C. Madge, *Tetrahedron*, 1989, **45**, 789.

- 7 R. S. J. Clark, A. B. Holmes and V. G. Matassa, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1389.
- 8 R. S. J. Clark, A. B. Holmes and V. G. Matassa, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1401.
- 9 R. A. Lee, *Tetrahedron Lett.*, 1973, 3333.
- 10 K. B. White and W. Reusch, *Tetrahedron*, 1978, **34**, 2439.
- 11 D. Spitzner, *Tetrahedron Lett.*, 1978, 3349.
- 12 M. H. Roberts and R. H. Schlessinger, *J. Am. Chem. Soc.*, 1981, **103**, 724.
- 13 R. Sutherland, E. A. P. Croydon and G. N. Rolinson, *Br. Med. J.*, 1970, **4**, 455.
- 14 R. J. Stedman, J. R. E. Hoover, A. W. Chow, M. M. Dolan, N. M. Hall and R. J. Ferlanto, *J. Med. Chem.*, 1964, **7**, 251.

Paper 0/05477A

Received 5th December 1990

Accepted 2nd January 1991
