Synthesis of the First Optically Active anti-Bredt Rule Compound with Known Absolute Configuration: (—)-(5*S*)-Bicyclo[3.3.1]non-1-ene

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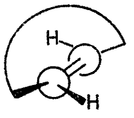
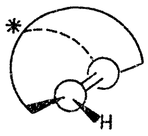
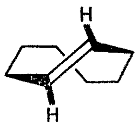
Summary The first optically active anti-Bredt rule compound, (—)-(5*S*)-bicyclo[3.3.1]non-1-ene (**4**) was prepared from (—)-(1*R*,3*S*)-*cis*-3-hydroxycyclohexanecarboxylic acid (**5**).

The bicyclic anti-Bredt rule hydrocarbon[1] (**2**) with a single-unsaturated centre can schematically be constructed from a *trans*-cycloalkene (**1**) by bridging [dotted line in (**2**)] the olefinic carbon atom and the *trans*-bridge. This bridging degrades the original C_2 symmetry inherent in the *trans*-cycloalkene to C_1 symmetry creating a new asymmetric centre (*) at the ring juncture.


(1)


(2)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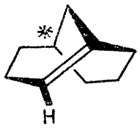
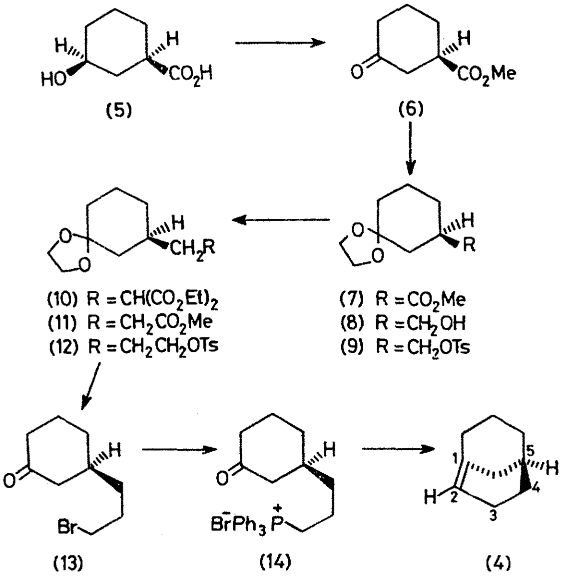

(4)

There seems to have been no explicit discussion of this intrinsic chiral nature of anti-Bredt rule compounds, and we here report the preparation of the first optically active anti-Bredt rule hydrocarbon with known absolute configuration, (—)-(5*S*)-bicyclo[3.3.1]non-1-ene[2] (**4**) which can be regarded as a methylene-bridge derivative of (−)-(*R*)-*trans*-cyclo-octene[3] (**3**).

Esterification with diazomethane followed by Jones oxidation converted the carboxylic acid[4] (**5**), $[\alpha]_D$ −6·2° (*c* 1·61, EtOH) (optical purity 36%),†‡ into (−)-(**6**), $[\alpha]_D$ −3·8° (*c* 2·46, EtOH), whose carbonyl group was protected by conversion into the (−)-acetal (**7**), $[\alpha]_D$ −15·2° (*c* 0·823, EtOH). Routine side chain extension procedure involving reduction with $LiAlH_4$, tosylation, and malonate ester synthesis converted the acetal (**7**) into the malonate (**10**) *via* (**8**) and (**9**). Saponification, decarboxylation, and re-esterification of the resulting carboxylic acid transformed (**10**) into (−)-(**11**), $[\alpha]_D$ −0·64° (*c* 5·33, EtOH), and reduction with $LiAlH_4$, followed by tosylation furnished the tosylate (**12**). Refluxing (**12**) with lithium bromide in acetone for 43 h yielded (+)-(**13**), $[\alpha]_D$ +3·0° (*c* 1·45, EtOH), which was converted into (+)-(**14**), $[\alpha]_D$ +3·6° (*c* 0·827, CH_2Cl_2). The final step in the synthesis was the intramolecular Wittig reaction[2] of (+)-(**14**) by heating with sodium hydride in tetraglyme (2,5,8,11,14-pentaoxapentadecane). Chromatography on Florisil of the olefinic product afforded a 27% yield of the bicyclic olefin (**4**), b.p. 80—85 °C at 12 mmHg, $[\alpha]_D$ −259° (*c* 0·574, $CHCl_3$), *m/e* 122 (M^+) whose identity was confirmed by spectroscopic comparison (i.r. and ^1H n.m.r.) with the racemic compound.[2]



The absolute rotation $[\alpha]_{D,abs.}$ for (**4**) was calculated to be −720° ($CHCl_3$), based on the estimated optical purity of the starting material, and this value can be compared with the reported value $[\alpha]_{D,abs.}$ −458° (neat) of (−)-(*R*)-*trans*-cyclo-octene[3] (**3**).

Their close stereochemical relationship is also revealed in their respective Cotton curves with $[\theta]_{213\,nm}$ $-1{\cdot}36 \times 10^5$ (*c* $9{\cdot}11 \times 10^{-4}$, iso-octane)§ for (**4**) and $[\theta]_{196nm}$ $-1{\cdot}41 \times 10^5$ (cyclohexane)[5] for (**3**), which are compatible with the prediction from Scott's octant projection.[5]

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† Structural assignments are supported by analytical and spectroscopic data.

‡ Conversion of the (+)-enantiomer of (**5**), $[\alpha]_D$ +5·6° (*c* 0·930, EtOH), into (−)-3-methylcyclohexanone, $[\alpha]_D$ −4·1° (*c* 1·62, EtOH) (optical purity 33%), gave the absolute rotation of the hydroxycarboxylic acid (**5**) as $[\alpha]_{D,abs.}$ −17·0°. Three absolute rotation values for 3-methylcyclohexanone have been reported: $[\alpha]_D$ 12·5° (H. L. Goering and E. F. Silversmith, *J. Amer. Chem. Soc.*, 1955, **77**, 5172); 11·7° (A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 1947, 205); and 13·54° (H. Rupe, *Annalen*, 1927, **459**, 206). The average absolute rotation, $[\alpha]_D$ 12·6°, was used in our optical purity calculations.

§ The $[\theta]$ value is corrected to 100% optical purity from the known optical purity.

[1] G. Köbrich, *Angew. Chem. Internat. Edn.*, 1973, **12**, 464; R. Keese, *ibid.*, 1975, **14**, 528; G. L. Buchanan, *Chem. Soc. Rev.*, 1974, **3**, 41.
[2] For the synthesis of the racemic compound, see K. B. Becker, *Helv. Chim. Acta*, 1977, **60**, 81, and references therein.
[3] A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, and H. J. S. Winkle, *J. Amer. Chem. Soc.*, 1963, **85**, 3276; A. C. Cope and A. S. Mehth, *ibid.*, 1964, **86**, 5626.
[4] W. Klyne and J. Buckingham, 'Atlas of Stereochemistry,' Chapman and Hall, London, 1974, p. 42.
[5] A. I. Scott and A. D. Wrixon, *Tetrahedron*, 1970, **26**, 3695.