Stereocontrolled Synthesis of Isocomene by a Novel Photocycloaddition–Fragmentation Strategy

Viresh H. Rawal,* Claire Dufour and Andrew Eschbach

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA

Isocomene has been synthesized in a stereocontrolled manner by a novel strategy that utilizes a Paterno–Büchi reaction to build complexity and a selective reductive fragmentation to reveal a functionalized diquinane.

The triquinane family of natural products includes a variety of structural types, such as propellanes, linear triquinanes, and angular triquinanes. Considerable effort has been expended on the synthesis of these challenging structures and elegant solutions have been provided.[1] We have developed a new, general strategy to linear and angular triquinanes and report here its successful implementation resulting in the stereocontrolled syntheses of the angular triquinane (±)-isocomene and a formal synthesis of (±)-β-isocomene.[2]

The major challenge in the synthesis of isocomene **1** lies in the construction of its unique skeleton, with control of its three contiguous quaternary centres and the tertiary methyl group.[3,4] Diquinane enone **3**, which has three of the stereocentres correctly in place, was envisioned to be a key intermediate to the isocomenes (Scheme 1). A 5-*exo* cyclization of the three-carbon chain onto the enone moiety would generate in one step the tricyclic framework and the last of the quaternary centres. *In situ* trapping of the resulting enolate as a triflate would provide precursor **2**, coupling of which with dimethyl copper lithium would allow the introduction of the last methyl group. Enone **3** was expected to be formed from the reductive fragmentation of ketoalkene **4**, which was available from norbornene **5**.

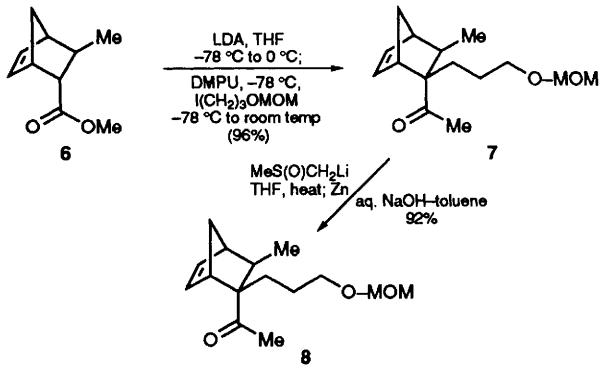
Norbornene **5** was prepared from the known cycloadduct of methyl crotonate and cyclopentadiene.† The enolate of ester **6** was treated with the methoxy methyl (MOM) ether of 3-iodopropan-1-ol in the presence of DMPU, which gave the desired alkylation product in 96% yield (Scheme 2). The reaction was remarkably *exo* selective (>15:1) despite the presence of the *exo*-methyl group on the adjacent carbon. Although ester **7** was resistant to basic hydrolysis, it was easily converted to the methyl ketone under the Corey procedure (dimsyl lithium, THF, 0 °C to 50 °C; quench with Zn, aq. NaOH–toluene, 92%).[5] The conversion of the norbornane skeleton of **8**, which has in place two of the four isocomene stereocentres, to a diquinane was accomplished efficiently *via* our photocyclization–reductive fragmentation sequence.[2]

Irradiation of methyl ketone **8** with Corex filtered light provided oxetane **9** in 92% yield (Scheme 3). The oxetane ring was cleaved using an excess of Pr^i_2NMgI (4–5 equiv., THF) at 50 °C. The resulting alcohol was converted into the desired fragmentation precursor (**10**) under the Swern[6] conditions (80% yield, two steps). The pivotal reductive–fragmentation was carried out using lithium di-*tert*-butylbiphenylide (LDBB) as the reducing agent.[7] As anticipated from the model studies,[2] the fragmentation was regiospecific and gave diquinane **11** in 60–65% yield (Scheme 3). The photocyclization–fragmentation sequence nicely transposes the *exo*-oriented substituents in norbornene **8** onto the convex face of diquinane **11**.

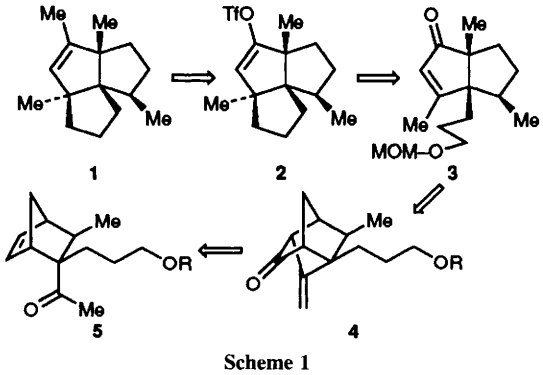
The requisite bridgehead methyl group was introduced by alkylation of the kinetic enolate (2 equiv. LDA, THF) with excess MeI in the presence of DMPU‡ (92% yield). In preparation for the closure of the last ring, the MOM group was removed using $LiBF_4$ in refluxing MeCN–water (95% yield).[8] Alcohol **12** can be converted under standard conditions to either bromide **13** (NBS, Ph_3P, CH_2Cl_2, 84% yield) or iodide **14** (Ph_3P, I_2, imidazole, THF, 98% yield).

The cyclization of these halides was accomplished under a variety of conditions. Interestingly, treatment of the bromide with 3 equiv. of LDBB at −78 °C resulted in the formation of the expected tricyclic ketone (**15**, 86%, Scheme 4), a compound which has been converted to (±)-β-isocomene (**16**) by a Wittig methylenation.[9]§ Ketone **15** was also formed by subjecting the bromide to standard radical cyclization conditions (Bu^n_3SnH, AIBN, PhH, heat, 91%).

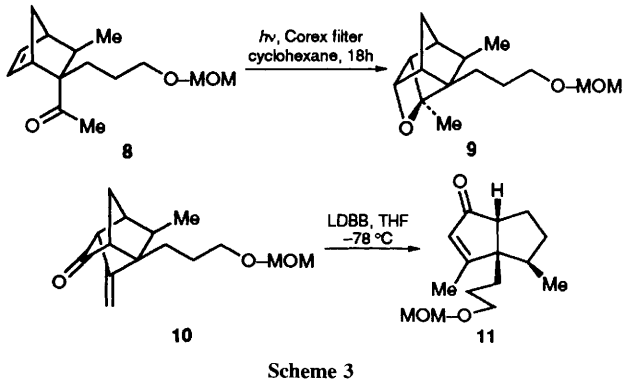
In an effort to develop a direct route to isocomene from a diquinane precursor, we examined protocols for anionic cyclization followed by *in situ* trapping of the resulting enolate. This transformation was accomplished by treatment of iodide **14** with Bu^nLi (1.1 equiv., −100 °C, THF)[10] and, after stirring for 10 min, quenching the reaction mixture with



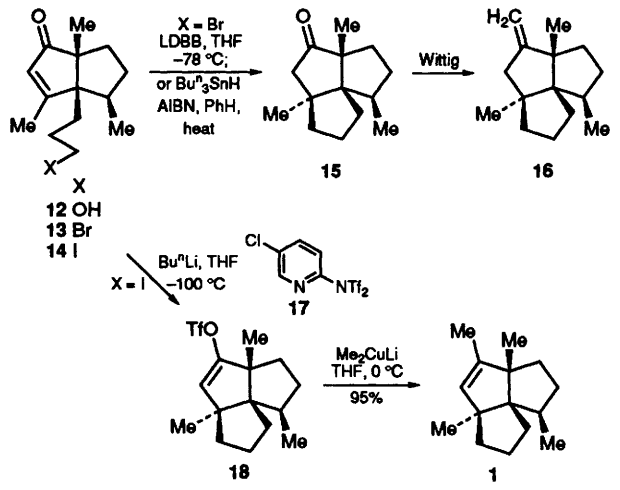
Scheme 2



Scheme 1



Scheme 3



Scheme 4

pyridine-derived triflating agent **17**.[11]¶ In this way enoltriflate **18** was obtained in one step in 76% yield. Completion of the synthesis of isocomene required only the replacement of the triflate with a methyl group. Cuprate coupling under the standard conditions proceeded very sluggishly,[12] presumably because of the steric congestion in this tricyclopentanoid. However, at a higher temperature (0 °C rather than −15 °C) and with an excess of Me_2CuLi (10 equiv.), the desired target, (±)-isocomene, was isolated in excellent yield. ‖

The synthesis of isocomene described here illustrates the applicability of our unique photocycloaddition–reductive fragmentation strategy to complex triquinane natural products. The synthetic sequence is relatively short and high-yielding (>25% overall), and should provide access to optically pure (−)-isocomene as well as related triquinane natural products.

This work was supported in part by The Ohio State University Office of Research and Graduate Studies. Dr Seiji Iwasa is thanked for invaluable technical assistance. V. H. R. thanks the American Cancer Society for a Junior Faculty Research Award (1990–1993) and Eli Lilly for a Lilly Granteeship.

Received, 10th May 1994; Com. 4/02775B

Footnotes

† The direct preparation of norbornene **5** through a Diels–Alder reaction between cyclopentadiene and the appropriate α,β-disubstituted dienophile was inefficient, giving predominantly the *exo* adduct.

‡ DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

§ This one-step cyclization trapping protocol appears to have considerable scope for the synthesis of a variety of complex molecules.

¶ The synthesis of **15** also represents a formal synthesis of isocomene, since acid-catalysed isomerization converts β-isocomene to isocomene. See ref. 8.

‖ The spectral data of our synthetic isocomene compared well to that reported in the literature. Comparison of the ^{1}H NMR (60 MHz) spectrum with that kindly furnished by Professor Paquette showed identical shifts for the four methyl groups (δ 0.86, 1.03, 1.04, 1.56) and the vinylic proton (δ 4.85).

References

1 L. A. Paquette and A. M. Doherty, *Polyquinane Chemistry: Syntheses and Reactions*, Springer–Verlag, New York, 1987, pp. 1–230.
2 V. H. Rawal and C. Dufour, *J. Am. Chem. Soc.*, 1994, **116**, 2613.
3 Isolation: L. H. Zalkow, R. N. Harris, III, D. Van Derveer and J. A. Bertrand, *J. Chem. Soc., Chem. Commun.*, 1977, 456; L. H. Zalkow, R. N. Harris, III and N. I. Burke, *J. Nat. Prod.*, 1979, **42**, 96; F. Bohlmann, N. Le Van and J. Pickardt, *Chem. Ber.*, 1977, **110**, 3777.
4 Syntheses: W. Oppolzer, K. Battig and T. Hudlicky, *Helv. Chim. Acta*, 1979, **62**, 1493; *Tetrahedron*, 1981, **37**, 4359; L. A. Paquette and Y. K. Han, *J. Am. Chem. Soc.*, 1981, **103**, 1835; *J. Org. Chem.*, 1979, **44**, 4014; M. C. Pirrung, *J. Am. Chem. Soc.*, 1979, **101**, 7130; 1981, **103**, 82; W. G. Dauben and D. M. Walker, *J. Org. Chem.*, 1981, **46**, 1103; P. A. Wender and G. B. Dreyer, *Tetrahedron*, 1981, **37**, 4445; E. Wenkert and T. S. Arrhenius, *J. Am. Chem. Soc.*, 1983, **105**, 2030; B. C. Ranu, M. Kavka, L. A. Higgs and T. Hudlicky, *Tetrahedron Lett.*, 1984, **25**, 2447; G. G. G. Manzardo, M. Karpf and A. S. Dreiding, *Helv. Chim. Acta*, 1986, **69**, 659; L. Fitjer, A. Kanschik and M. Majewski, *Tetrahedron Lett.*, 1988, **29**, 5525, and ref. 9.
5 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345; J. S. Swenton, D. K. Anderson, D. K. Jackson and L. Narasimhan, *J. Org. Chem.*, 1981, **46**, 4825; K. Ishizumi, N. Ohashi and N. Tanno, *J. Org. Chem.*, 1987, **52**, 4477.
6 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165; K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651.
7 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924; C. Rücker, *Tetrahedron Lett.*, 1984, **25**, 4349; *J. Organomet. Chem.*, 1986, **310**, 135; S. D. Rychnovsky and D. E. Mickus, *Tetrahedron Lett.*, 1989, **30**, 3011; T. Cohen, I. Jeong, B. Mudryk, M. Bhupathy and M. M. A. Awad, *J. Org. Chem.*, 1990, **55**, 1528.
8 B. H. Lipshutz and D. F. Harvey, *Synth. Commun.*, 1982, **12**, 267; R. E. Ireland and M. D. Varney, *J. Org. Chem.*, 1986, **51**, 635.
9 Y. Tobe, T. Yamashita, K. Kakiuchi and Y. Odaira, *J. Chem., Chem. Commun.*, 1985, 898.
10 M. P. Cooke, Jr., *J. Org. Chem.*, 1992, **57**, 1495 and references cited therein.
11 **17**: *N*-(5-chloro-2-pyridyl)triflimide; D. L. Comins and A. Delhangi, *Tetrahedron Lett.*, 1992, **33**, 6299. See also: J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.
12 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1980, **21**, 4313; Review: W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, 1988, **21**, 47.