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George A. Kraus
Iowa State University, gakraus@iastate.edu

Yung Son Hon
Iowa State University

James Sy
Iowa State University

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Abstract

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Disciplines

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Synthesis of Bicyclo[3.2.1]octanes by Ring Contraction

George A. Kraus,* Yung-Son Hon, and James Sy

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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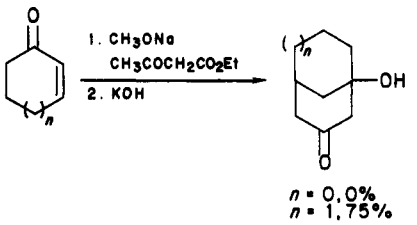
Two methods for the formation of the bicyclo[3.2.1]octane system by ring contraction of bicyclo[3.3.1]nonan-3-ones are described. One method uses the Büchi ring contraction. The other method uses the oxidative cleavage of an alkene followed by an aldol cyclization.

The bicyclo[3.2.1]octane system is a common subunit in many natural products. It is present in diterpene families such as the kaurenes and the gibberellins and also in many sesquiterpenes. As a consequence, many methods have been developed to construct the bicyclo[3.2.1]octane system. In most syntheses the two-carbon bridge is formed last. Examples include the facile intramolecular nitrone reactions of Funk and co-workers[1] and intramolecular alkylations of ketones, nitriles, and sulfones.[2] Trost has recently reported a clever synthesis of bicyclic ring systems using (2-bromoallyl)trimethylsilane.[3] Bicyclic ring formation by Diels–Alder reactions or by [4 + 3] cycloaddition reactions represents another successful strategy.[4] Büchi has reported a direct method for preparing highly functionalized bicyclo[3.2.1]octanes.[5] Additionally, the bicyclo[3.2.1]octane system can be generated by the rearrangement of a bicyclo[2.2.2]octane.[6] However, most of these methods are compatible with only a limited range of substituents at the bridgehead positions.

Many syntheses of natural products containing the bicyclo[3.2.1]octane system have been reported. In virtually every case the bicyclic system was formed in the middle or the latter stage of the synthetic pathway. One notable exception is the synthesis of gibberellin A_1 by Mander.[7] Our studies of bridgehead intermediates in synthesis[8] have shown that initial formation of the bridged bicyclic system followed by appendage of the requisite rings can be an attractive alternative. Our initial studies were done with the bicyclo[3.3.1]nonane system. It was prepared from a substituted cyclohexenone and ethyl acetoacetate by a Michael addition/aldol sequence. Unfortunately, this same sequence failed to produce bicyclo[3.2.1]octanes.[9] In view of the ready accessibility of bicyclo[3.3.1]nonanes, we examined the possibility of ring contraction to produce bicyclo[3.2.1]octanes.



(1)

Two methods[10] that appeared compatible with our systems were the Büchi ring contraction[11] and one based on oxidative cleavage of a double bond followed by an aldol condensation. The Büchi ring contraction conditions were examined first. This method has been used to prepare unsaturated ketones, esters, nitriles, and sulfones.[12]

(1) Funk, R. L.; Horcher, L. H. M.; Daggett, J. U.; Hansen, M. M. *J. Org. Chem.* **1983**, *48*, 2632.
(2) For ketones: Liu, H.-J.; Chan, W. H. *Can. J. Chem.* **1982**, *60*, 1081. For sulfones: Piers, E.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 1138.
(3) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879.
(4) Diels–Alder reaction: Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Am. Chem. Soc.* **1983**, *48*, 1146. For [4 + 3] additions: Hoffmann, H. M. R.; Henning, R. *Helv. Chem. Acta* **1983**, *66*, 828.
(5) Büchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *97*, 4509.
(6) Van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142.
(7) For an excellent review, see: Vandewalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767. The Mander synthesis: Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626.
(8) Bridgehead carbocations: Kraus, G. A.; Hon, Y.-S. *J. Am. Chem. Soc.* **1985**, *107*, 4341. Kraus, G. A.; Hon, Y.-S. *J. Org. Chem.* **1985**, *50*, 4605. Bridgehead enones: Kraus, G. A.; Hon, Y.-S., submitted for publication in *J. Org. Chem.*
(9) Momose, T.; Muraoka, O. *Chem. Pharm. Bull.* **1978**, *26*, 288. The Michael addition step actually works well, the problem step is the aldol reaction.
(10) For a good reference for ring contractions in steroid chemistry, see: *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. 2, pp 408–448.
(11) Büchi, G.; Hochstrasser, U.; Pawlak, W. *J. Org. Chem.* **1973**, *38*, 4348.

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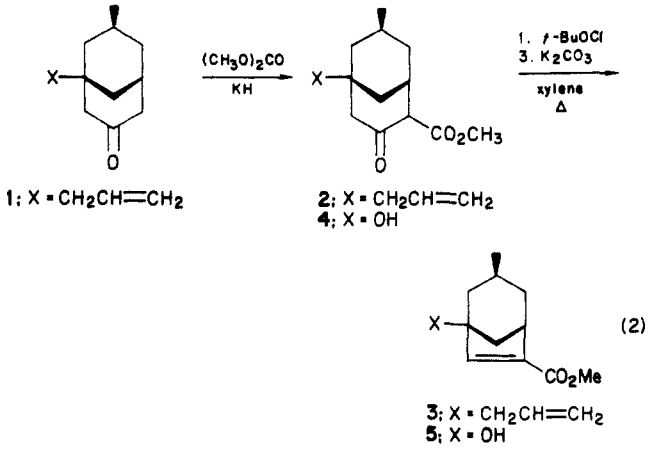
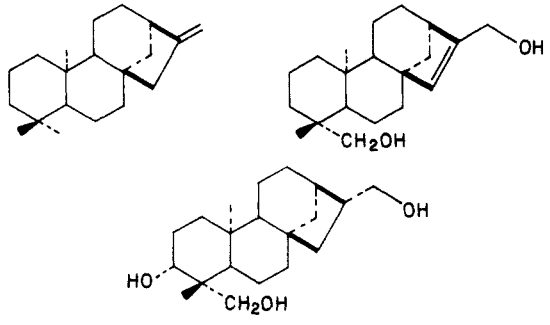
However, to the best of our knowledge, this method has not been used in bridged systems. Keto ester **2** was prepared from **1**[13] by treatment of the olefinic ketone with dimethyl carbonate in the presence of potassium hydride. Keto ester **2** was then subjected to the Büchi procedure, namely, chlorination with *t*-BuOCl followed by heating the crude product with sodium carbonate in the presence of glass beads in boiling xylene. Ester **3** was produced in 79% overall yield. In the same manner, keto ester **4**[14] afforded hydroxy ester **5** in 81% yield. Notably, no product derived from a retroaldol reaction was observed. The unsaturated



(2)

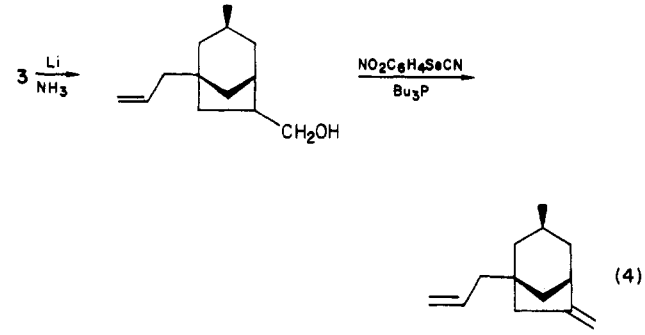
ester in **4** and **5** is an excellent precursor for the functionality in the two-carbon bridge of the bicyclo[3.2.1]octane unit of most diterpenes. Both kaurene and gibberellin A_{15} have an exomethylene group in the two carbon bridge. Kauran-17-oic acid has a saturated carboxylic acid in its two-carbon bridge. Other functional groups that have



(3)

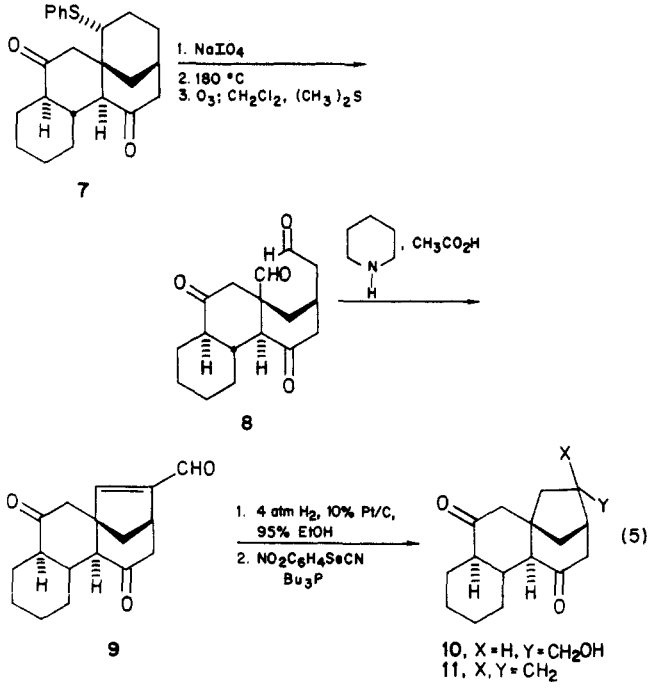
been found in this position include the hydroxymethyl group and the allylic alcohol moiety.[15] Reduction of unsaturated ester **5** with an excess of lithium in liquid ammonia afforded alcohol **6**. This could be eliminated to provide an exomethylene group by using the method of Grieco.[16]

The ring contraction method based on the oxidative cleavage of a double bond has been employed several times in less complex systems. This method was used by Corey in his classic synthesis of helminthosporal.[17] In this case a synthetic intermediate containing a bicyclo[3.3.1]nonane subunit was oxidatively cleaved with $OsO_4/NaIO_4$ and then cyclized to produce a bicyclo[3.2.1]octane unit. This me-



(4)

thod was tried on ketone **7**[a] which was derived from a Diels–Alder reaction on a bridgehead enone. The alkene was formed by pyrolysis of the corresponding sulfoxide. Because of the unfavorable steric interactions produced in order to achieve the transition state for sulfoxide elimination, an unusually high temperature was required. The



(5)

optimum conditions involved the pyrolysis of the sulfoxide in a sealed tube in carbon tetrachloride containing aqueous calcium carbonate. The alkene was formed in 60% yield. The alkene could be readily cleaved with ozone in methylene chloride at −78 °C. The reaction was quenched with dimethyl sulfide at −78 °C. In this reaction the choice of solvent was critical. If methanol or methanol in methylene chloride was used, several byproducts were formed. The dialdehyde **8** was then subjected to several cyclization conditions. While the reaction with titanium tetrachloride and TAMA[18] worked well on a small scale, cyclization with piperidinium acetate[19] eventually became the method of choice. Unsaturated aldehyde **9** could be reduced to the saturated alcohol **10** with 10% Pt/C in ethanol. This compound could then be converted to the alkene **11** by using the method of Grieco.[16]

The bicyclo[3.3.1]nonane system can be transformed into the bicyclo[3.2.1]octane system by two different ring contraction schemes. The ease of formation of substituted bicyclo[3.3.1]octanes coupled with the ring contraction

(12) For examples of the preparation of unsaturated ketones and esters, see ref 11. For the preparation of unsaturated nitriles, see: Herter, R.; Fohlisch, B. *Ber.* **1982**, *115*, 381.
(13) Kraus, G. A.; Hon, Y.-S. *J. Org. Chem.* **1985**, *50*, 4605.
(14) Heumann, A. *Synthesis* **1979**, 53.
(15) For an excellent compilation, see: Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic: New York, 1972.
(16) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(17) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1963**, *85*, 3527.
(18) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *J. Am. Chem. Soc.* **1982**, *104*, 872.
(19) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

experiments described herein greatly increase the usefulness of the bicyclo[3.3.1]nonane system as a synthetic precursor to polycyclic natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 60-MHz instrument and on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument. High-resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

1-Allyl-4-carbomethoxy-7-methylbicyclo[3.3.1]nonan-3-one (2). To a flask containing potassium hydride (1.73 mmol) was added a mixture of compound 1 (0.144 g, 0.75 mmol) and 2.5 mL of dimethyl carbonate at room temperature under nitrogen. The mixture was stirred at room temperature overnight. It was then poured into cold aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed with 10:1 hexanes–ethyl acetate to yield 0.152 g of product (81% yield): ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.3 Hz, 3 H), 0.9–2.9 (m, 13 H), 3.75 (s, 3 H), 5.1 (m, 2 H), 5.8 (m, 1 H); IR ($CDCl_3$) 3060, 1740, 1700, 1430, 1285, 1100, 980 cm^{-1}.

Büchi Ring Contraction. General Procedure. To a 1 M solution of keto ester (1 equiv) in methanol at −15 °C under nitrogen was added a 1 M solution of *tert*-butyl hypochlorite (1.1 equiv) in methanol. The mixture was then cooled in the refrigerator overnight and then stirred at rrom temperature for 4 h. The mixture was then concentrated to afford a crude product, which was taken on to the next step without purification. To a 0.2 M solution of the crude product (1 equiv) in xylene were added glass beads and sodium carbonate (1 equiv). The mixture was then heated to reflux for 12 h. The mixture was cooled, filtered through Celite, and then concentrated. The crude product was chromatographed on silica gel. The overall yields for 3 and 5 were 72% and 81%, respectively.

1-Allyl-3-carbomethoxy-7-methylbicyclo[3.2.1]oct-2-ene (3): ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1–3.0 (m, 10 H), 3.72 (s, 3 H), 5.05 (m, 2 H), 5.8 (m, 1 H), 6.6 (s, 1 H); ^{13}C NMR ($CDCl_3$) 21.65, 26.47, 33.04, 39.02, 40.19, 42.47, 48.77, 49.55, 51.24, 117.25, 134.55, 137.47, 147.81, 165.31 ppm; IR ($CDCl_3$) 3070, 2950, 1710, 1640, 1610, 1455, 1260, 1225, 1195, 1080, 910, 780 cm^{-1}; HRMS, m/e for $C_{14}H_{20}O_2$ requires 220.14633, measured 220.1469.

1-Hydroxy-3-carbomethoxybicyclo[3.2.1]oct-2-ene (5): ^{1}H NMR ($CDCl_3$) δ 1.1–3.2 (m, 9 H), 3.72 (s, 3 H), 6.60 (s, 1 H); IR (film) 3440, 3060, 2960, 1740, 1710, 1610, 1445, 1140, 880, 735 cm^{-1}; mass spectrum; m/e 55, 67, 81, 95, 108, 123, 140, 153, 167, 182.

3-(Hydroxymethyl)bicyclo[3.2.1]octan-1-ol (6). To 35 mL of liquid ammonia was added a solution of 5 (0.235 g, 1.29 mmol) and *tert*-butyl alcohol (0.478 g, 6.45 mmol) in 3 mL of THF. To the resulting solution was added lithium (0.070 g, 10 mmol) in pieces. The solution was stirred at −33 °C for 2 h and quenched with ammonium chloride, and then the ammonia was allowed to evaporate. The crude mixture was neutralized with 3 N HCl and extracted with CH_2Cl_2. The organic layer was dried and concentrated. The crude product was chromatographed with ethyl acetate to afford 0.082 g of product (41% yield): ^{1}H NMR ($CDCl_3$) δ 1.00–2.80 (m, 12 H), 3.70 (d, J = 8 Hz, 2 H). IR ($CDCl_3$) 3400, 2960, 1440, 1330, 1260, 1090, 1020, 810, 720 cm^{-1}.

Sulfide Oxidation and Elimination. The sulfide was oxidized with sodium periodate in methanol at room temperature. The crude sulfoxide (0.283 g, 0.74 mmol) was heated at 180 °C for 24 h in a two-phase reaction of carbon tetrachloride (5 mL) and water (1 mL) containing 0.148 g of calcium carbonate. The reaction was conducted in a sealed tube. The crude product was purified by flash chromatography using 5:1 hexanes–ether to afford a 58% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.95–2.90 (m, 20 H), 5.32–5.45 (m, 1 H), 5.61–5.68 (m, 1 H); IR (film) 2930, 1680–1700 (br), 1440, 1095, 900 cm^{-1}; mass spectrum, m/e 258.

Ozonolysis and Cyclization To Produce Aldehyde 9. To a solution of the alkene (0.060 g, 0.23 mmol) in 2 mL of methylene chloride at −78 °C was passed ozone until a pale blue color appeared. The solution was purged with nitrogen, and then 2 mL of dimethyl sulfide was added at −78 °C. The reaction was allowed to warm to room temperature and was then concentrated. The crude dialdehyde was unstable and was taken on to the next step without purification. To a solution of the crude dialdehyde (0.038 g, 0.13 mmol) in 1 mL of dry benzene were added two drops of piperidine and three drops of acetic acid. The solution was heated at 70 °C overnight, cooled, and concentrated. The crude product was purified by silica gel chromatography to afford a 46% overall yield of 9: ^{1}H NMR ($CDCl_3$) δ 0.95–3.02 (m, 16 H), 3.20–3.45 (m, 2 H), 6.58 (s, 1 H), 9.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) 25.22, 25.39, 25.64, 33.92, 37.72, 43.71, 46.50, 48.38, 50.91 53.59, 56.62, 61.76, 150.86, 151.09, 188.11, 206.23, 209.19; mass spectrum, m/e 91, 107, 120, 162, 230, 272; HRMS; m/e for $C_{17}H_{20}O_3$ found 272.1422, calcd 272.14125.

Acknowledgment. We thank the National Institutes of Health for generous financial support.

Registry No. (±)-1, 96791-72-9; 2, 102537-76-8; (±)-3, 102537-77-9; 4, 102537-78-0; (±)-5, 102537-79-1; 6, 102537-80-4; (±)-7, 102537-81-5; (±)-7 (alkene), 102537-82-6; (±)-7 (sulfoxide), 102537-84-8; (±)-8, 102537-85-9; (±)-9, 102537-83-7.

Coupling of Aryl Chlorides by Nickel and Reducing Metals

Ismael Colon* and Donald R. Kelsey

Technical Research Center, Union Carbide Corporation, Bound Brook, New Jersey 08805

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An efficient synthesis of biaryls (diarenes) from aryl chlorides has been developed and investigated. The coupling reagent is a catalytic mixture of anhydrous nickel salt and triphenylphosphine in the presence of a reducing metal (Zn, Mg, or Mn). The reaction occurs rapidly under mild conditions, tolerates a variety of functional groups, employs air-stable starting materials, and can be run conveniently in ordinary laboratory glassware. Excess reducing metal drives the coupling process and allows even aryl chlorides to be coupled to high yields, a distinguishing advantage over previous coupling processes which employed stoichiometric zero-valent nickel reagents. The reaction is pseudo-zero-order in aryl chloride and is promoted by 2,2′-bipyridine and by halide salts (F < Cl < Br < I). A number of reaction variables have been examined and their effects on the kinetics and yields are discussed. Reduction and aryl transfer from triphenylphosphine, the major side reactions, can be minimized in most cases. A coupling mechanism consistent with the observed kinetics and reaction parameters is proposed in which the key step is reduction of an arylnickel species by zinc to an arylnickel(I) complex.

Aryl–aryl carbon bonds are formed by many methods which require metals.[1] Examples are direct oxidative dehydrodimerization by Pd,[2] V,[3] Cu,[4] and Tl[5] and reductive coupling with loss of a substituent group, as in the

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