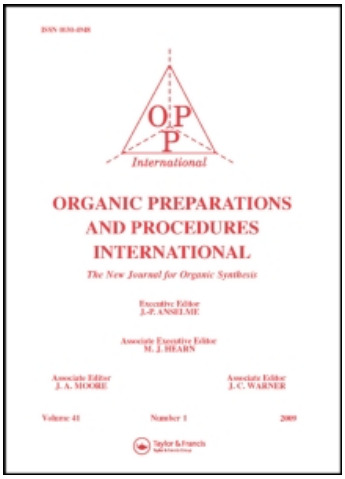


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF BICYCLO[2,1,1]HEXANE-1-CARBOXYLIC ACID

Rawyani S. Abeywickrema[a]; Ernest W. Della[a]
[a] School of Physical Sciences Flinders University, Bedford Park, South Australia

To cite this Article Abeywickrema, Rawyani S. and Della, Ernest W.(1980) 'AN IMPROVED SYNTHESIS OF BICYCLO[2,1,1]HEXANE-1-CARBOXYLIC ACID', Organic Preparations and Procedures International, 12: 6, 357 — 360
To link to this Article: DOI: 10.1080/00304948009356490
URL: http://dx.doi.org/10.1080/00304948009356490

ORGANIC PREPARATIONS AND PROCEDURES INT. 12(6), 357-360 (1980)

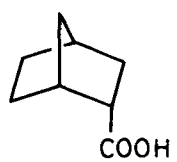
AN IMPROVED SYNTHESIS OF BICYCLO[2,1,1]HEXANE-1-CARBOXYLIC ACID

Ramyani S. Abeywickrema and Ernest W. Della*

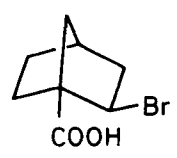
School of Physical Sciences
Flinders University
Bedford Park, South Australia, 5042

Undoubtedly the most convenient entry into bridgehead-substituted polycycloalkanes is via the corresponding carboxylic acid. Such is the case not only because of the versatility of the carboxyl group, which is readily converted into a variety of other functional groups including halogen, amine, and hydroxyl, but also because the acid is frequently obtained by ring contraction involving a Favorski-type rearrangement. We required several derivatives of the bicyclo[2,1,1]hexane system, most of which we planned to prepare from bicyclo[2,1,1]hexane-1-carboxylic acid 1.

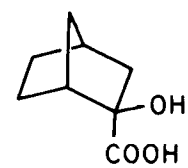
1



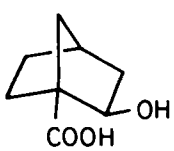
2



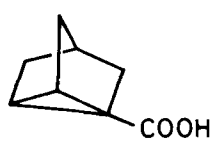
3



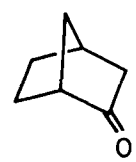
4



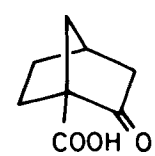
5



6



7

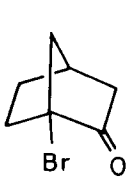


8

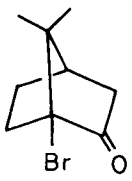
The acid 1 was first obtained some time ago by Wiberg and his associates[1] by a twelve-step synthesis from norbornanone. In view of the tedious

nature of this route, its extremely low yield, coupled with the fact that it is not especially adaptable to large scale synthesis, we developed an alternative method which obviates these difficulties and which we now wish to report.

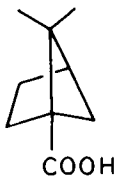
Bromination of *endo*-bicyclo[2,2,1]heptane-2-carboxylic acid 2, which is obtained by hydrogenation of the Diels-Alder adduct of cyclopentadiene and acrylic acid, produces *exo*-2-bromobicyclo[2,2,1]heptane-1-carboxylic acid 3[2]. Hydrolysis of 3 occurs under mild conditions to give a 3:9:1 mixture of the acids 4, 5, and 6. The hydroxy acids 4 and 5 were found to be easily separable from 6 by virtue of their water-solubility, and were oxidised by chromic acid to the ketone 7 and the ketoacid 8 respectively.



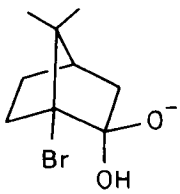
9



10



11



12

Brominative decarboxylation of the latter yielded a 6:1 mixture of the bromoketone 9 and norbornanone. These could be separated by distillation, but in practice the presence of norbornanone did not affect the conversion of 9 in high yield into the desired acid 1 by base-promoted ring contraction. This sequence proceeds in a 14% yield overall from the *endo*-acid 2.

The final step is noteworthy inasmuch as an attempt[4] to induce rearrangement of the related compound 10 under similar conditions produced very little (ca. 4%) of the acid 11. At extremely high dilution and under much more drastic conditions 10 afforded 11 in better yield (ca. 40%). This presumably reflects the significantly higher steric hindrance by the bridge methyl groups to formation of the intermediate adduct 12 from 10.

The acid 1 was converted smoothly into 1-bromobicyclo[2,1,1]hexane (71%) under the conditions employed[5] for other bridgehead acids.

EXPERIMENTAL

2-Ketobicyclo[2,2,1]heptane-1-carboxylic Acid (8). — 2-*Exo*-bromobicyclo-[2,2,1]heptane-1-carboxylic acid[2] (40g, 0.18 mol) was added to a solution of sodium hydrogen carbonate (50g) in water (210 ml) and the mixture heated at 70-75° with occasional swirling for 1 hour. The solution was cooled to 5°, acidified (pH 3) with 6N HCl and then extracted with hexane in order to remove 6 (1.4g ; 5.6%). The aqueous layer was saturated with NaCl and extracted with ether (4 x 80 ml). The combined ether extracts were dried ($MgSO_4$), and evaporated to give an oil (24.5g) which was redissolved in ether (100 ml) and treated dropwise, with stirring, with chromic acid solution (30g $Na_2Cr_2O_7$, 22.5 ml concentrated H_2SO_4 made up to 150 ml with water). Stirring was continued for 24 hours after which the ether layer was separated and the aqueous phase saturated with NaCl and extracted with fresh solvent. The combined ether layers were shaken with saturated $NaHCO_3$ solution and the layers separated. The organic phase contained norbornanone (3.2g, 16%). The aqueous layer was acidified and extracted with ether as above to give a white solid which upon sublimation (100°/0.1 mm) followed by recrystallisation from 1:2 ether-pentane yielded colourless needles of 8 (14.1g, 50%), m.p. 126-127° (lit.[3] 128-128.5°); nmr ($CDCl_3$): δ 1.4-2.4 (m, 8H), 2.6-2.9 (m, 1H, bridgehead proton), 11.1 (s, 1H, COOH); mass spectrum m/e 154 (M^+).

1-Bromobicyclo[2,2,1]heptan-2-one (9). — A stirred mixture of the keto-acid 8 (5.0g, 32 mmol), red mercuric oxide (7.5g, 34 mmol) and anhydrous $MgSO_4$ (3.0g) in dichloromethane (60 ml) was heated to reflux and treated dropwise over a 45-minute period with a solution of bromine (6.5g, 41 mmol) in dichloromethane (5 ml). The stirred mixture was maintained under reflux for a further 2 hours, and then cooled and filtered. The filtrate

was washed successively with 15% KI solution and 15% $Na_2S_2O_3$ solution, then dried ($MgSO_4$) and evaporated. The residue was shown (glc : QF-1) to consist of a 6:1 mixture of the bromoketone 9 and norbornanone. Distillation (95-98°/5 mm) afforded 9 (4.8g, 78%) contaminated with a small quantity (ca. 2%) of norbornanone. Preparative glc (SE 30) gave pure 9, n_D^{25} 1.5265; IR (neat): 1760; nmr ($CDCl_3$): δ1.5-2.3 (m, 8H), 2.5-2.8 (m, 1H, bridgehead proton); mass spectrum m/e 190 and 188 (M^+).

Anal. Calcd. for C_7H_9BrO : C, 44.47; H, 4.80

Found : C, 44.16, H, 4.85

Bicylco[2,1,1]hexane-1-carboxylic Acid (1). — The bromoketone 9 (2.5g; 0.013 mole) was boiled with 12% KOH (200 ml) for 48 hours. The resulting solution was cooled, neutralised (pH 7), and extracted with ether. The aqueous layer was further acidified (pH 2) with 4N HCl and extracted with ether. The ether extracts were dried ($MgSO_4$), and the solvent evaporated giving a solid which on sublimation (70°/0.1 mm) followed by recrystallisation from pentane gave the acid 1 (1.4g, 84%), mp 46° (lit.[1] 46-50.1°).

The acid (1.86g) in dichloromethane (35 ml) containing a suspension of red HgO (3.4) was treated with bromine (2.8g) under the conditions specified above. The solvent was removed by distillation through a column packed with glass helices, and the residue distilled giving 1-bromobicyclo-[2,1,1]hexane (1.7g, 71%), bp. 140-143° (lit.[1] 140-141°); mass spectrum m/e 162 and 160 (M^+).

REFERENCES

1. K. B. Wiberg, B. R. Lowry, and T. H. Colby, J. Am. Chem. Soc., 83, 3998 (1961); K. B. Wiberg and B. R. Lowry, ibid., 85, 3188 (1963).
2. W. E. Boehme, ibid., 81, 2762 (1959) and earlier papers cited therein.
3. W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, ibid., 87, 2204 (1965).
4. W. C. Fong, R. Thomas, and K. V. Scherer, Jr., Tetrahedron Lett., 3789 (1971).
5. E. W. Della and H. K. Patney, Synthesis, 751 (1976).

(Received December 10, 1979; in revised form March 24, 1980)