A synthesis of α-cuparenone based on symmetry considerations

Tse-Lok Ho and May-Hua Chang

Abstract: A ring expansion approach to α-cuparenone was accomplished in 5 or 6 steps. The key intermediate is 3-methyl-3-(4-methylphenyl)cyclobutanone, which was derived from a [2+2]cycloaddition of dichloroketene on a styrene derivative, followed by dechlorination.

Key words: symmetry, α-cuparenone, ring expansion, sesquiterpene.

Résumé : On a réalisé une synthèse de l'α-cuparénone en 5 ou 6 étapes par le biais d'une extension de cycle. L'intermédiaire clé est la 3-méthyl-3-(4-méthylphényl)cyclobutanone obtenue par une cycloaddition [2+2] du dichlorocétène sur un dérivé du styrène, suivie d'une déchloration.

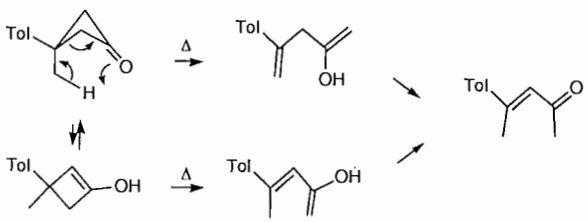
Mots clés : symétrie, α-cuparénone, extension de cycle, sesquiterpène.

[Traduit par la rédaction]

Cuparene (**1**) is one of the simplest sesquiterpenes. Its synthetic challenge lies in the presence of two contiguous quaternary carbon centers on a cyclopentane unit. Our interest in the pursuit of a cuparene synthesis stemmed from symmetry considerations (1).

The ring expansion theme formed the basis of several previous approaches (for details, see ref. 2). However, we thought that routes traversing a symmetrical cyclobutanone intermediate would offer distinct advantages by avoiding any regiochemical problems due to indiscriminate C—C bond migration in the ring expansion step. In other words, extra caution of design is not needed to avoid production of regioisomeric cyclopentane derivatives. Accordingly, we started our work by a [2+2]cycloaddition of α,*p*-dimethylstyrene with dichloroketene under ultrasonic irradiation. The adduct **2**, obtained in 76% yield, was dechlorinated with zinc dust and sodium iodide in glacial acetic acid at 80–90°C to afford 3-methyl-3-(4-methylphenyl)cyclobutanone (**3**) in 84% yield. Originally we failed to achieve this transformation using zinc dust alone, zinc–copper couple, or aluminum amalgam as reducing agent; therefore sodium iodide appears to have played a critical role in the reduction. Interesting also is an adventitious observation of ring cleavage to provide dehydrocurcumone on heating **3** to temperatures above 190°C. We can attribute this transformation either to a bond reorganization reminiscent of a McLafferty rearrangement, the driving force being relief of ring strain, or to an electrocyclic reversion via the enol species (eq. [1]). With the symmetrical ketone **3** at hand, the stage was set for ring expansion (3). Reaction of **3**

[1]



with [tris(methylthio)methyl]lithium afforded a mixture of *cis* and *trans* hydroxythioorthoesters **4A/4B**, in a combined yield of 94%. The more polar isomer was considered to have the tolyl and the tris(methylthio)methyl groups disposed in a *trans* relationship because 2D-NMR indicated a nuclear Overhauser effect of the *S*-methyl substituents with the benzylic methyl. Both **4A** and **4B** were elaborated with equal efficiency to the same product **5** on treatment of the corresponding lithium alkoxide with copper(I) perchlorate – acetonitrile complex; therefore in the preparative routine we could perform this step using the stereoisomeric mixture.

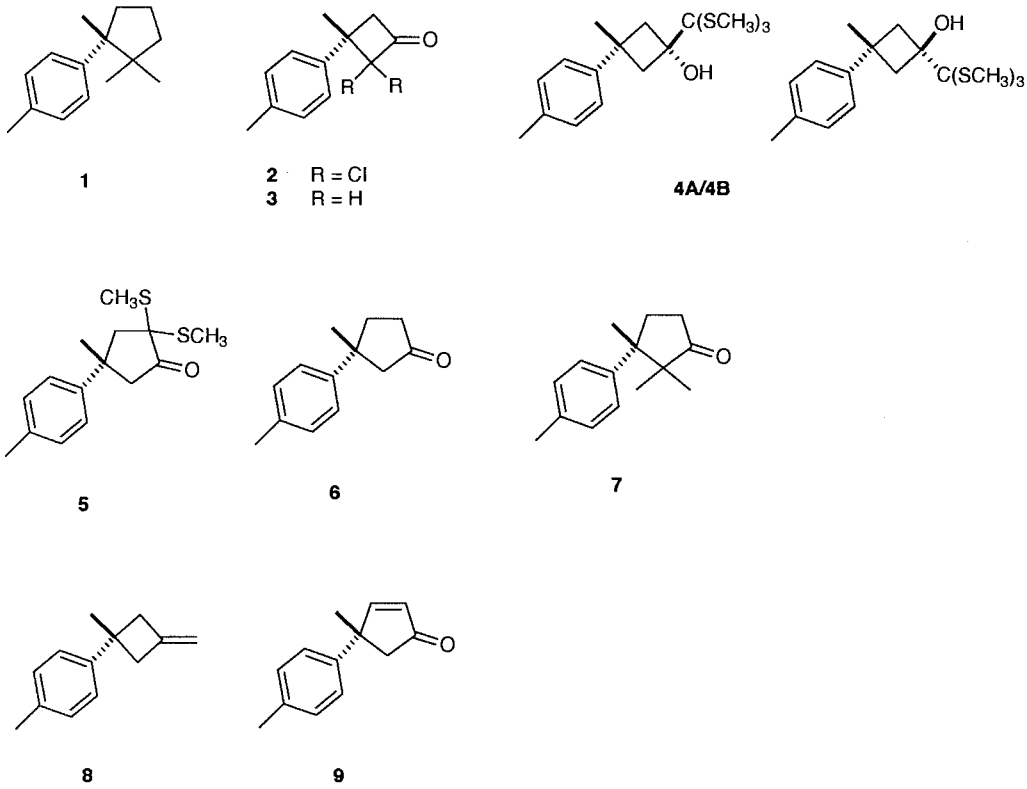
At the outset, it was our intention to exploit the blocking of the appropriate α-methylene group by the bis(methythio) unit in **5** to achieve the desired *gem*-dimethylation in a regioselective fashion. Several attempts were made to perform the transformation with various bases (NaH, *t*-BuOK, LDA) and methylating agents (MeI, Me_2SO_4) but, unfortunately, the desired product could not be obtained in acceptable yield. The reaction was complicated by elimination of one methanethiol molecule, presumably after *S*-methylation, and also by enol methylation. In hindsight it may be reasonable to attribute this behavior to steric hindrance by a methylthio group to the approach of the electrophile. Both faces of the cyclic enolate intermediate were shielded by substituents of two quaternary centers. The pathway involving methanethiol elimination apparently did not fare any better, the enolate species being a *cisoid* 2,3-disubstituted diene in which the bulky groups are

Received October 24, 1996.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

T.-L. Ho[1] and M.-H. Chang. Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China.

[1] Author to whom correspondence may be addressed. Telephone: 886-35-712121, ext. 56538. Fax: 886-35-723764.

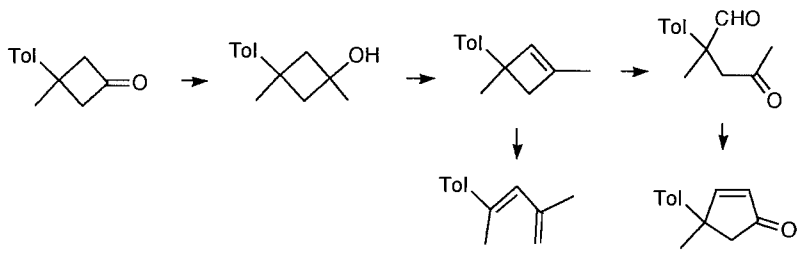


forced to adopt a coplanar conformation. Formation of such an enolate must be quite unfavorable.

Reports (4) that 3-methyl-3-arylcyclopentanones undergo methylation at C-2 with good selectivity ensured us an escape, although the yield was low (26%) and we were still disappointed at the failure of our original design. Desulfurization of **5** with Raney nickel in refluxing ethanol furnished ketone **6** in 85% yield, and the methylation proceeded to give α-cuparenone (**7**). α-Cuparenone is a well-known synthetic precursor of cuparene; therefore our work also represents a formal synthesis of the hydrocarbon.

An alternative and more direct method for the conversion of **3** to **6** is by Wittig reaction followed by treatment of the methylenecyclobutane derivative **8** with thallium(III) nitrate trihydrate (5). We also considered a route in which **3** was subjected to reaction with methylmagnesium iodide, dehydration, ozonolysis, and aldolization (eq. [2]) to reach another known precursor **9** of α-cuparenone. On preliminary investigations we found this last reaction sequence to be much inferior, the cyclobutene intermediate being rather prone to ring opening by electrocyclic reversion.

In conclusion, we have evaluated the concept of symmetry by an expedient route to α-cuparenone.



[2]

Experimental

General

Infrared spectra (IR) were obtained from neat film on KBr disks using a Jasco FT/IR-200 spectrometer. Mass spectra were measured with a TRIO-2000 or JEOL JMS-HX110 instrument. Proton and carbon nuclear magnetic resonance spectra in deuterochloroform solutions were determined by a Varian Unity-300 spectrometer. The following abbreviations were indicated: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Materials

Anhydrous sodium sulfate was used for drying organic solutions during work-up of reactions. Thin-layer chromatography was performed on aluminum-backed silica gel plates with fluorescent coating. Separation by column chromatography was performed on silica gel 60 as supplied by E. Merck.

2,2-Dichloro-3-methyl-3-(4-methylphenyl)cyclobutanone (2)

A two-necked round-bottom flask was charged with α,*p*-dimethylstyrene (2.26 g, 17.1 mmol) and zinc dust (2.4 g, 36.7 mg-atm) in anhydrous ether (50 mL). The flask, equipped with a rubber septum and a condenser topped with a drying

tube, was placed in an ultrasonic cleaning bath. While maintaining the temperature of the bath water below 20°C by occasional addition of ice during irradiation, trichloroacetyl chloride (3.0 mL, 26.9 mmol) was introduced slowly into the flask via a syringe. At the end of 3 h, the reaction mixture was diluted with more ether, filtered through Celite, and washed with sodium carbonate solution. Removal of the ether from the dried solution and evaporative distillation gave **2** (3.16 g, 76% yield). IR: 1811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ δ: 1.63 (s, 3H), 2.37 (s, 3H), 3.05 (d, 1H, J = 16 Hz), 3.96 (d, 1H, J = 16 Hz), 7.16 (d, 1H, J = 8 Hz), 7.22 (d, 2H, J = 8 Hz). HRMS, *m/z*: 242.0271, 244.0236, 246.0203 (calcd. for $C_{12}H_{12}OCl_2$: 242.0257, 244.0227, 246.0197).

3-Methyl-3-(4-methylphenyl)cyclobutanone (3)

A mixture of dichloroketone **2** (0.50 g, 2.06 mmol), sodium iodide (0.77 g, 5.14 mmol), and zinc dust (0.34 g, 5.2 mg-atm) in glacial acetic acid (6 mL) was magnetically stirred and maintained between 80 and 90°C for 11 h. On cooling to room temperature, water and dichloromethane were added to the reaction mixture. The organic layer was washed with sodium carbonate solution, dried, and evaporated to give a residue that was filtered through a short column of silica gel, affording **3** (0.30 g, 84% yield). IR: 1795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 3H), 2.36 (s, 3H), 3.07 (d, 2H, J = 16 Hz), 3.42 (d, 2H, J = 16 Hz), 7.16 (d, 2H, J = 8.4 Hz), 7.18 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.9 (q), 31.0 (q), 33.5 (s), 59.15 (t), 125.4 (d), 129.1 (d), 135.5 (s), 145.2 (s), 205.4 (s). HRMS, *m/z*: 174.1027 (calcd. for $C_{12}H_{14}O$: 174.1045).

3-Methyl-3-(4-methylphenyl)-1-[tris(methylthio)]-methylcyclobutanols (4A/4B)

A magnetically stirred solution of tris(methylthio)methane (1.40 g, 9.1 mmol) in dry THF (15 mL) at −78°C was treated with *n*-butyllithium (2.5 M in hexane, 3.6 mL, 9.0 mmol). After 0.5 h, ketone **3** (1.06 g, 6.1 mmol) was introduced via a syringe. The reaction was allowed to proceed for 1.5 h, quenched with a mixture of glacial acetic acid (0.6 mL) and ethanol (6 mL), and the cooling bath was removed. When room temperature was reached, the reaction mixture was distributed between CH_2Cl_2 and water; the organic solution was washed with aqueous sodium bicarbonate, dried, and concentrated in vacuo to provide a 1:1 mixture of products **4A** and **4B** (1.87 g, 94% yield), which were separated by silica gel chromatography.

The less polar isomer: IR: 3481 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.56 (s, 3H), 2.23 (s, 9H), 2.34 (s, 3H), 2.35 (d, 2H, J = 18.6 Hz), 2.93 (d, 2H, J = 18.6 Hz), 3.64 (s, 1H, OH), 7.25 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0 (q), 20.8 (q), 27.1 (q), 41.7 (t), 42.4. (s), 75.7 (s), 81.1 (s), 124.1 (d), 128.8 (d), 135.1 (s), 146.0) (s). HRMS, *m/z*: 328.0946, 281.1066 (calcd. for $C_{16}H_{24}OS_3$: 328.0991, for $C_{15}H_{21}OS_2$: 281.1035).

The more polar isomer: IR: 3480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36 (s, 3H), 2.17 (s, 9H), 2.25 (s, 3H), 2.46 (dd, 2H, J = 13.2, 2.7 Hz), 2.77 (dd, 2H, J = 13.2, 2.7 Hz), 3.02 (s, 1H, OH), 7.07 (d, 2H, J = 8.1 Hz), 7.19 (d, 2H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.9 (q), 20.9 (q), 32.7 (q), 35.9 (s), 47.1 (t), 76.6 (s), 79.1 (s), 125.5 (d), 128.9 (d), 134.7 (s), 147.3 (s). EIMS, *m/z*: 328 ($M^{+\cdot}$).

2,2-Bis(methylthio)-3-methyl-3-(4-methylphenyl)-cyclopentanone (5)

To a solution of **4A/4B** (0.25 g, 0.76 mmol) in toluene (40 mL) cooled to −78°C was added by syringe *n*-butyllithium (1.6 M in hexane, 0.6 mL, 0.94 mmol). After 0.5 h, tetrakis(acetonitrile)copper(I) perchlorate (0.55 g, 1.68 mmol) was added in one portion, and the cooling bath was then removed to allow the reaction to proceed at room temperature for 1.5 h, after which it was heated to 78°C for 2 h. The reaction mixture was quenched with a mixture of aqueous NH_4Cl–NH_4OH (pH 8), cooled to room temperature, filtered, and extracted with ether. After washing with water, drying, concentration, and chromatography, **5** was obtained (0.14 g, 64% yield). IR: 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 3H), 1.99 (s, 3H), 2.10 (s, 3H), 2.26 (s, 3H), 2.45 (d, 2H, J = 16.8 Hz), 2.59 (d, 2H, J = 7.5 Hz), 2.60 (d, 2H, J = 7.5 Hz), 3.21 (d, 2H, J = 16.8 Hz), 7.08 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.4 (q), 13.0 (q), 20.9 (q), 31.5 (q), 40.5 (s), 49.1 (t), 51.5 (t), 62.5 (s), 125.0 (d), 129.2 (d), 135.9 (s), 145.8 (s), 207.4 (s). HRMS, *m/z*: 280.0949 (calcd. for $C_{15}H_{20}OS_2$: 280.0957).

3-Methyl-3-(4-methylphenyl)-1-methylenecyclobutane (8)

A solution of ketone **3** (0.94 g, 5.4 mmol) in ether (2 mL) was added to the Wittig reagent prepared from methyltriphenylphosphonium bromide (1.785 g, 5 mmol) in anhydrous ether (10 mL) by treatment with *n*-butyllithium (1.43 M, 3.5 mL, 5 mmol) for 5 min at room temperature. The mixture was stirred overnight, filtered, and the residue was triturated with ether. The organic solution was evaporated, and the product was purified by silica gel chromatography to afford **8** (0.865 g, 93% yield). IR: 1687, 876, 816 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.53 (s, 3H), 2.37 (s, 3H), 2.73 (d, 2H, J = 13.5 Hz), 3.08 (d, 2H, J = 13.5 Hz), 4.90 (s, 2H), 7.12 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1 (q), 30.5 (q), 38.3 (s), 44.9 (t), 107.3 (t), 125.8 (d), 128.7 (d), 134.7 (s), 144.6 (s), 147.7 (s). EIMS; *m/z*: 172 ($M^{+\cdot}$).

3-Methyl-3-(4-methylphenyl)cyclopentanone (6)

From 5

A suspension of Raney nickel (ca. 2 mL) was washed three times with ethanol. A solution of **5** (114 mg, 0.41 mmol) in ethanol (6 mL) was added and the mixture was refluxed under nitrogen overnight. The metal was filtered, the filtrate was evaporated, and the residue was chromatographed to provide ketone **6** (65 mg, 85% yield). IR: 1741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ δ: 1.33 (s, 3H), 2.18–2.33 (m, 4H), 2.30 (s, 3H), 2.40 (d, 1H, J = 18 Hz), 2.58 (d, 1H, J = 18 Hz), 7.11 (d, 2H, J = 6 Hz) 7.14 (d, 2H, J = 6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7 (q), 29.2 (q), 35.7 (t), 36.5 (t), 43.2 (s), 52.1 (t), 125.1 (d), 129.0 (d), 135.5 (s), 145.2 (s), 218.5 (s). HRMS, *m/z*: 188.1185 (calcd. for $C_{13}H_{16}O$: 188.1202).

From 8

A mixture of the methylenecyclobutane **8** (0.10 g, 0.58 mmol) and thallium(III) nitrate trihydrate (0.26 g, 0.58 mmol) in methanol (6 mL) was stirred at room temperature for 12 h. At this point solid NaCl (0.17 g) was added, the solid was filtered after 10 min, and the filtrate was evaporated in vacuo, redissolved in CH_2Cl_2, washed with brine, then water, dried, and concentrated. The product was purified by silica gel chromatography to give **6** (0.074 g, 68% yield).

α-Cuparenone (7)

Prepared in 26% yield by methylation according to ref. 4. IR: 1741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.60 (s, 3H), 1.16 (s, 3H), 1.25 (s, 3H), 1.85 (m, 1H), 2.33 (s, 3H), 2.3–2.7 (m, 3H), 7.06 (d, 2H, J = 7.8 Hz), 7.18 (d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.4 (q), 20.8 (q), 22.1 (q), 25.3 (q), 29.6 (t), 33.6 (t), 48.3 (s), 53.1 (s), 126.3 (d), 128.9 (d), 135.6 (s), 141.8 (s), 221.9 (s). EIMS, *m/z*: 216 ($M^{+\cdot}$).

Acknowledgment

We thank the National Science Council of the Republic of China (ROC) for financial support of the project.

References

1. T.-L. Ho. Symmetry. A basis for synthesis design. Wiley, New York. 1995.
2. T.-L. Ho. Evolution of synthetic pathways. Parallax and calibration. World Scientific Publ., Singapore. 1996. pp. 61–63.
3. S. Knapp, A.F. Trope, M.S. Theodore, N. Hirata, and J. Barchi. J. Org. Chem. **49**, 608 (1984).
4. G.H. Posner and C.M. Lentz. J. Am. Chem. Soc. **101**, 934 (1979); T. Kametani, K. Kawamura, M. Tsubuki, and T. Honda. Chem. Pharm. Bull. **33**, 4821 (1985); M. Asaoka, K. Takenouchi, and H. Takei. Tetrahedron Lett. **29**, 325 (1988).
5. D. Farcasiu, P.v.R. Schleyer, and D.B. Ledlie. J. Org. Chem. **38**, 3455 (1973).

This article has been cited by:

1. Erika Leemans, Matthias D'hooghe, Norbert De Kimpe. 2011. Ring Expansion of Cyclobutylmethylcarbenium Ions to Cyclopentane or Cyclopentene Derivatives and Metal-Promoted Analogous Rearrangements. *Chemical Reviews* **111**:5, 3268-3333. [CrossRef]
2. Jesús Armando Luján-Montelongo, José G. Ávila-Zárraga. 2010. Palladium (II) catalyzed 5-endo epoxynitrile cyclizations: total syntheses of enokipodins A and B. *Tetrahedron Letters* **51**:17, 2232-2236. [CrossRef]
3. Nan-Yan Fu, Siu-Hin ChanThe Application of Cyclobutane Derivatives in Organic Synthesis . [CrossRef]
4. Raymond L. Funk, Spencer KnappTris(methylthio)methane . [CrossRef]
5. Tse-Lok Ho, Chun-Kuei Chen. 2006. Synthesis of Tangutorine. *Helvetica Chimica Acta* **89**:1, 122-126. [CrossRef]
6. Tse-Lok Ho, Chun-Kuei Chen. 2005. Synthesis of Eburnamine, Isoeburnamine, and Eburnamoninevia a Spirocyclic Intermediate. *Helvetica Chimica Acta* **88**:10, 2764-2770. [CrossRef]
7. T.-L. HO, M.-H. CHANG. 1997. ChemInform Abstract: A Synthesis of α-Cuparenone Based on Symmetry Considerations. *ChemInform* **28**:52, no-no. [CrossRef]