2,2-Dimethyl cyclopentanones by acid catalyzed ring expansion of isopropenylcyclobutanols. A short synthesis of (±)-α-cuparenone and (±)-herbertene†

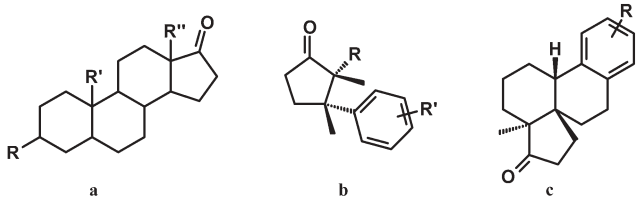
Angela M. Bernard, Angelo Frongia, Francesco Secci and Pier P. Piras*

Received (in Cambridge, UK) 25th April 2005, Accepted 27th May 2005
First published as an Advance Article on the web 23rd June 2005
DOI: 10.1039/b505707h

2,2-Dimethyl cyclopentanones are readily prepared by acid catalyzed ring expansion of isopropenylcyclobutanols; the method allows ready access to the family of sesquiterpenes cuparanes and herbertanes, as demonstrated by the synthesis of (±)-α-cuparenone and the direct precursor of (±)-herbertene.

2,2-Dialkyl-substituted cyclopentanones and cyclopentanes are present in a wide variety of natural products. Their structures characterize the core of different classes of substances like steroids **a**, sesquiterpenes **b**, spirocyclic and/or [c] fused systems **c** (Scheme 1).

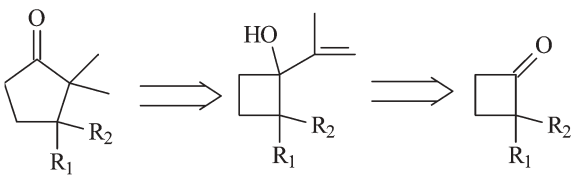
Particularly important members of the above mentioned family are the 2,2-dimethyl substituted cyclopentanones and cyclopentanes. As a matter of fact these latter members are present in the carbon skeleton of the sesquiterpenes of the cuparane and herbertane families,[1] characterized by the presence of a sterically congested 1-aryl-1,2,2-trimethylcyclopentane moiety, several of which possess biological properties. Moreover the 2,2-dimethyl substituted cyclopentanones and cyclopentanes are present in some other cuparene-type sesquiterpenes like grimaldone and epigrimaldone first isolated from the central European liverwort *Mannia fragrans*,[2] and those isolated from a mycelia culture of *Flammulina velutipes*,[3] some of which show antimicrobial activity. 2,2-Dimethyl substituted cyclopentanone or cyclopentanol frameworks are present in the modified estrogens C-nor-9,11-secoestranes[4] and in some other products used as intermediates in the synthesis of natural derivatives.[5] Concerning their synthesis, as well as that of 2,2-dialkyl-cyclopentanones, the alkylation of cyclopentanones is not amenable for large scale preparation as this reaction is plagued by side reactions like aldol condensation, regioisomer formation due to equilibration among 2-alkylcyclopentanone enolates and polyalkylation.[6] A possible way to overcome the above synthetic problems could be the acid catalyzed ring expansion of a suitably substituted isopropenylcyclobutanol,[7] easily obtainable from the corresponding cyclobutanone, as shown in the retrosynthetic analysis of Scheme 2.



Scheme 1

Unfortunately this acid catalyzed ring expansion, well known in the 1-vinylcyclopropanol series, is reported to be a sluggish reaction, in the absence of a sulfur substituent, in the 1-vinylcyclobutanol series.[8] Nevertheless, the fact that we recently discovered[9] that the ring expansion of the isopropenylcyclobutanol **6g** (Table 1) to the corresponding 2,2-dimethylcyclopentanone **7g** could be carried out very cleanly in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, encouraged us to plan the use of these reaction conditions for the synthesis of some 2,2-dimethyl substituted cyclopentanones, with the final goal of preparing some sesquiterpenes of the cuparane and herbertane families. The synthetic plan (Scheme 3) involves the formation of the alcohols **2a–f** by reaction of lithium cyclopropylphenyl sulfide with the corresponding ketone or aldehyde **1a–f** and its ring expansion to cyclobutanone **3a–f** by refluxing in wet benzene in the presence of an equimolar amount of PTSA. On the other hand cyclobutanones **3g,h** were prepared, according to our previous reported results,[9] by lithium iodide catalyzed ring enlargement of the oxaspiropentanes **5g,h** obtained by oxidation of the alkylidenecyclopropanes **4g,h**.

The use of this different protocol was dictated by the fact that ring expansion of the cyclopropylcarbinols, obtained by reaction of lithium cyclopropylphenylsulfide with the corresponding ketones, leads to chromene derivatives by capture of the intermediate cyclobutylthionium carbocation.[10] The cyclobutanones **3a–h** were then reacted with isopropenyl magnesium bromide to give the corresponding cyclobutanols **6a–h** as a mixture of geometric isomers except for **6b–d** where only the *cis* isomer was detected on the basis of NOE experiments. Finally



Scheme 2 Retrosynthetic analysis for the synthesis of 2,2-dimethyl-cyclopentanones.

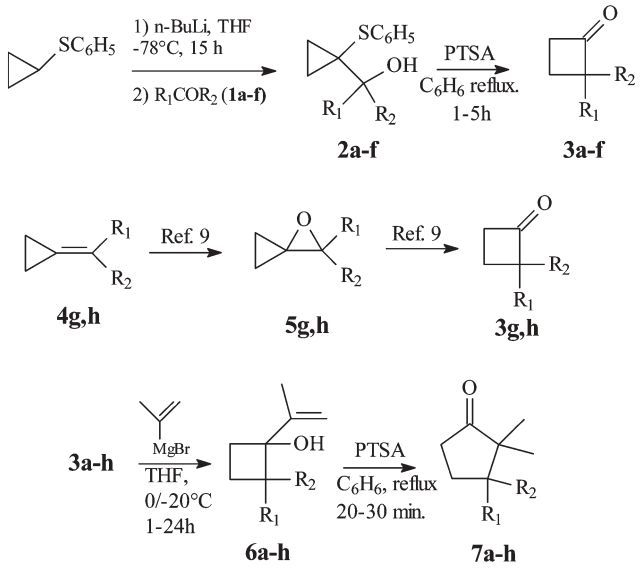
Dipartimento di Scienze Chimiche, Università di Cagliari, Complesso Universitario di Monserrato, S.S 554 Bivio per Sestu, I 09042, Monserrato (Cagliari), Italy. E-mail: pppiras@unica.it; Fax: +39 0706754388; Tel: +39 0706754410

† Electronic supplementary information (ESI) available: Detailed descriptions of experimental procedures and characterization of compounds **2f, 6a–f, 6h, 6l, 7a–d, 7h, 7l, 8b, 9i, 10i, 11i** and 2-bromo-6-phenyl-1-hexene. See http://dx.doi.org/10.1039/b505707h

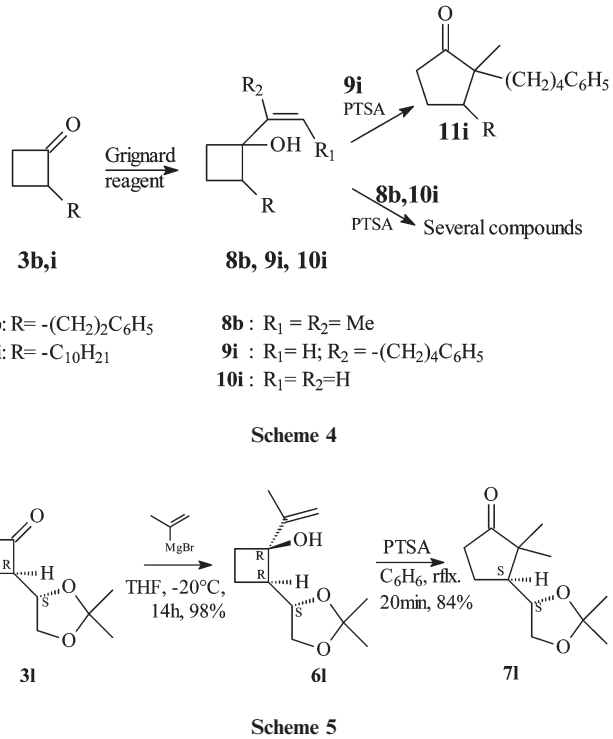
Table 1 Reaction of cyclobutanones **3** to give the cyclobutanols **6** and the cyclopentanones **7**

3	R_1	R_2	6 (Yield (%)); (*cis* : *trans* ratio)	7 (Yield (%))
3a	Me	$-(CH_2)_2C_6H_5$	**6a** (71) (69 : 31)	**7a** (71)
3b	H	$-(CH_2)_2C_6H_5$	**6b** (98) (100 : 0)	**7b** (98)
3c	H	$-CH(CH_3)CH_2SC_6H_5$	**6c** (98) (100 : 0)	**7c** (98) (50 : 50)
3d	H	$-C_6H_4$-*p*-Me	**6d** (95) (100 : 0)	**7d** (95)
3e	Me	$-C_6H_4$-*p*-Me	**6e** (76) (64 : 36)	**7e** (76) (±)-α-cuparenone
3f	Me	$-C_6H_4$-*m*-Me	**6f** (70) (50 : 50)	**7f** (70)
3g	Me	$-CH_2OC_6H_4$-*p*-OMe	**6g** (70) (38 : 62)	**7g** (70)[a]
3h	Me	$-CH_2OC_6H_4$-*m*-Me	**6h** (80) (25 : 75)	**7h** (80)[b]

[a] See ref. 9. The increased yield was obtained using one equivalent of PTSA. [b] Accompanied by 10% of the corresponding chromene by protonation of the alcohol and subsequent ring closure, like in ref. 9.



Scheme 3 Synthesis of cyclobutanols **6** and cyclopentanones **7**.



Scheme 4

Scheme 5

treatment of **6a–h** with a stoichiometric amount of PTSA in benzene gave good to excellent yields of the expected cyclopentanones **7a–h** (Table 1).

As a matter of fact, in this way we have realized the short synthesis of (±)-α-cuparenone **7e**[1h] and of the cyclopentanone **7f**[11] that is the direct precursor of (±)-herbertene.[11]

We also checked the possibility of using other differently substituted vinyl cyclobutanols to prepare other 2-alkyl or 2,2-dialkyl substituted cyclopentanones. For this purpose the cyclobutanones **3b,i** were treated with the corresponding vinylic Grignard reagents to obtain the cyclobutanols **8b, 9i, 10i** (Scheme 4). When treated with PTSA **8b** and **10i** failed to give the expected cyclopentanones, but led to a very complex mixture of several products, while **9i**[12] gave cleanly **11i** as a 60 : 40 mixture of geometric isomers.

As the asymmetric synthesis of **3e** has already been reported,[13] we were interested to check the stereochemistry of this pinacol-type rearrangement, to plan the synthesis of optically active **7e** and **7f**. For this purpose we treated the optically pure cyclobutanone **3l**,[14] to obtain the isopropenylcyclobutanol **6l** as a single diastereoisomer, whose *cis* stereochemistry was attributed analogously to our previously reported similar cyclobutanols.[15] Exposure of **6l** to the usual reaction conditions gave smoothly the interesting cyclopentanone **7l** as a single diastereoisomer, with no loss of stereochemical integrity of the migrating stereocenter (Scheme 5).[16]

This result confirms the possibility of the synthesis of derivatives **7** in a chiral non-racemic form, starting from optically active cyclobutanones **3**, whose synthesis is now in progress in our laboratory.

In summary we have reported a method for the synthesis of 2,2-dimethyl substituted cyclopentanones and used it for the preparation of some naturally occurring cuparanes and herbertanes. Moreover we have demonstrated that using our reaction conditions it should be possible to manage their synthesis in an optically active form.

Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and from the University of Cagliari [National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" (PRIN) and "Design, synthesis and biological and pharmacological evaluation of organic molecules as innovative drugs" (FIRB)] is gratefully acknowledged.

Notes and references

1 For some recent papers reporting on different members of these families see: (*a*) S. Acherar, G. Audran, F. Cecchin and H. Monti, *Tetrahedron*, 2004, **60**, 5907; (*b*) D. Ng, Z. Yang and M. A. Garcia-Garibay, *Org.*

Lett., 2004, **6**, 645; (*c*) A. Srikrishna, N. C. Babu and M. S. Rao, *Tetrahedron*, 2004, **60**, 2125; (*d*) S. P. Chavan, R. K. Kharul, R. R. Kale and D. A. Khobragade, *Tetrahedron*, 2003, **59**, 2737; (*e*) S. Acherar, G. Audran, N. Vanthuyne and H. Monti, *Tetrahedron: Asymmetry*, 2003, **14**, 2413; (*f*) T. Paul, A. Pal, P. D. Gupta and D. Mukherjee, *Tetrahedron Lett.*, 2003, **44**, 737; (*g*) Y. Kita, J. Futamura, Y. Ohba, Y. Salama, J. K. Ganesh and H. Fujioka, *Tetrahedron Lett.*, 2003, **44**, 411; (*h*) T. Satoh, M. Yoshida, Y. Takahashi and H. Ota, *Tetrahedron: Asymmetry*, 2003, **14**, 281; (*i*) B. R. Aavula, Q. Cui and E. A. Mash, *Tetrahedron: Asymmetry*, 2000, **11**, 4681; (*j*) T. Poon, B. P. Mundy, F. G. Favaloro, C. A. Goudreau, A. Greenberg and R. Sullivan, *Synthesis*, 1998, 832.

2 A. Srikrishna and D. B. Ramachary, *Tetrahedron Lett.*, 2000, **41**, 2231.

3 N. K. Ishikawa, K. Yamaji, S. Tahara, Y. Fukushi and K. Takahashi, *Phytochemistry*, 2000, **54**, 777.

4 K. Lal, I. Sharma, A. K. Agarwal, A. Agnihotri and S. Ray, *J. Med. Chem.*, 1988, **31**, 1261.

5 (*a*) R. D. Bowden, R. D. G. Cooper, C. J. Harris, G. P. Moss, B. C. L. Weedon and L. M. Jackman, *J. Chem. Soc., Perkin Trans. I*, 1983, 1465; (*b*) A. Ghosh, U. K. Banerjee and R. V. Venkateswaran, *Tetrahedron*, 1990, **46**, 3077; (*c*) D. Patra and S. Ghosh, *Synth. Commun.*, 1994, **24**, 1663; (*d*) S. Samajdar, A. Ghatak and S. Ghosh, *Tetrahedron Lett.*, 1999, **40**, 4401; (*e*) S. Samajdar, A. Ghatak, S. Banerjee and S. Ghosh, *Tetrahedron*, 2001, **57**, 2011.

6 H. O. House, *Modern Synthetic Reactions*, WA Benjamin, New York, 2nd edn., 1972, ch. 9; For a review see: J. K. Rasmussen, *Synthesis*, 1977, 91.

7 K. Estieu, J. Ollivier and J. Salaun, *Tetrahedron*, 1998, **54**, 8075.

8 (*a*) C. R. Johnson and R. W. Herr, *J. Org. Chem.*, 1973, **38**, 3153; (*b*) T. Cohen, L.-C. Yu and W. M. Daniewski, *J. Org. Chem.*, 1985, **50**, 4596; For related ring expansion using Pd see: (*c*) H. Nemoto, M. Shiraki and K. Fukumoto, *Tetrahedron*, 1994, **50**, 10391; (*d*) H. Nemoto, J. Miyata, M. Yoshida, N. Raku and K. Fukumoto, *J. Org. Chem.*, 1997, **62**, 7850; (*e*) B. M. Trost and T. Yasukata, *J. Am.Chem. Soc.*, 2001, **123**, 7162; For related iodonium ion-mediated ring expansion of olefinic cyclobutanols see: (*f*) H. Nemoto, M. Shiraki and K. Fukumoto, *Tetrahedron Lett.*, 1995, **36**, 8799; (*g*) H. Nemoto, M. Shiraki and K. Fukumoto, *J. Org. Chem.*, 1996, **61**, 1347.

9 A. M. Bernard, C. Floris, A. Frongia, P. P. Piras and F. Secci, *Tetrahedron*, 2004, **60**, 449.

10 A. M. Bernard, E. Cadoni, A. Frongia, P. P. Piras and F. Secci, *Org. Lett.*, 2002, **4**, 2565.

11 M.-L. Leriverend and M. Vazeux, *J. Chem. Soc., Chem. Commun.*, 1982, 866.

12 **9i** was prepared from the corresponding lithium derivative obtained from 2-bromo-6-phenyl-1-hexene (see ESI†).

13 (*a*) H. Nemoto, H. Ishibashi, M. Nagamochi and K. Fukumoto, *J. Org. Chem.*, 1992, **57**, 1707; (*b*) For the synthesis of an analogous cyclobutanone following a different procedure see: K. Hiroi, H. Nakamura and T. Anzai, *J. Am. Chem. Soc.*, 1987, **109**, 1249.

14 A. M. Bernard, A. Frongia, P. P. Piras and F. Secci, *Org. Lett.*, 2003, **5**, 2923.

15 A. M. Bernard, C. Floris, A. Frongia and P. P. Piras, *Tetrahedron*, 2000, **56**, 4555.

16 For a strictly related rearrangement see: N. Sarkar, A. Nayek and S. Ghosh, *Org. Lett.*, 2004, **6**, 1903.