Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8185–8188

Diverse carbocyclic systems using geminal acylation as a key process

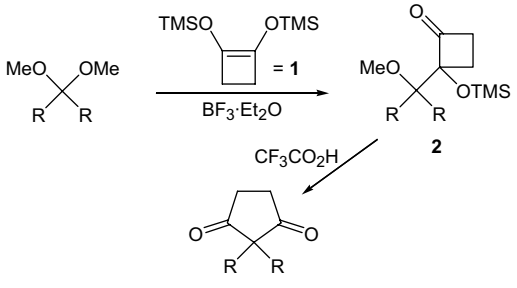
Fuye Gao and D. Jean Burnell*

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3

Received 22 June 2007; revised 12 September 2007; accepted 13 September 2007
Available online 18 September 2007

Abstract—Geminal acylation has been employed in the syntheses of a diquinane, a 1,3-diketone with herbicidal and pesticidal activity, and compounds with carbocyclic [5.16.5] and [5.17.5] skeletons.

Geminal acylation is a process by which ketones and aldehydes, or acetals derived from these, can be converted into 2-substituted 1,3-cycloalkanediones. The original report[1] used a two-step procedure with acetals. In the first step, the reaction with 1,2-bis(trimethylsilyloxy)cyclobutene **1**[2] in the presence of $BF_3{\cdot}Et_2O$ provided cyclobutanone **2**, and then rearrangement with a protic acid gave the 1,3-diketone (Scheme 1). Isolation of **2** can be obviated by the use of a large excess of the Lewis acid because in this medium the rearrangement also takes place.[3,4] Modification of this one-pot procedure led to successful geminal acylation of ketones.[5] The reactions of alkyl-substituted versions of **1**[6] and of the five-membered analogue of **1**[7] have been explored. Intramolecular geminal acylations were carried out,[8] and a procedure for the efficient geminal acylation of acetals derived from aldehydes was disclosed recently.[9]

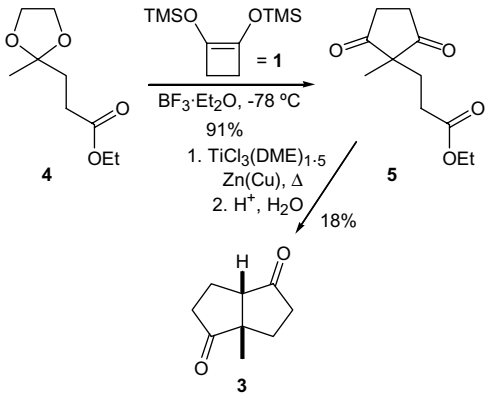


Scheme 1.

Geminal acylation has been used in a number of synthetic endeavors.[3,10]

We report here the use of geminal acylation in short sequences leading to compounds of interest in different fields.

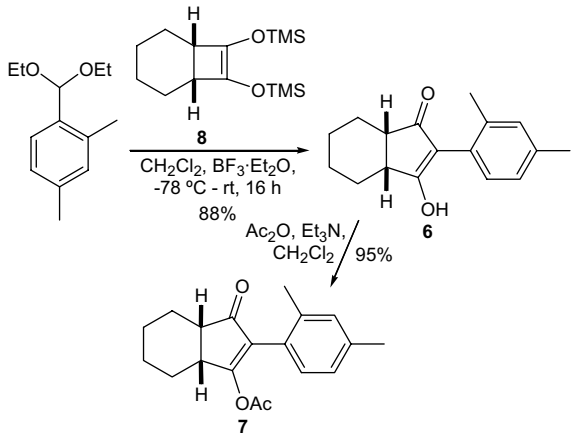
An enantiomer of diquinane **3** was prepared by Mehta and Acharyulu[11] by a nine-step sequence from limonene. The overall yield of the sequence was 7%. We have prepared **3**, in racemic form, in just three steps from commercially available ethyl levulinate (Scheme 2). The acetal of this compound, **4**, underwent geminal acylation with **1** in the presence of $BF_3{\cdot}Et_2O$ to give 1,3-diketone **5**.[4] (The geminal acylation of ethyl levulinate directly proceeds in only 36% yield.[5]) Low-valent titanium[12] was produced by reducing $TiCl_3(DME)_{1.5}$



Scheme 2.

* Corresponding author. Tel.: +1 902 494 1664; fax: +1 902 494 1310; e-mail: jean.burnell@dal.ca

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.09.089

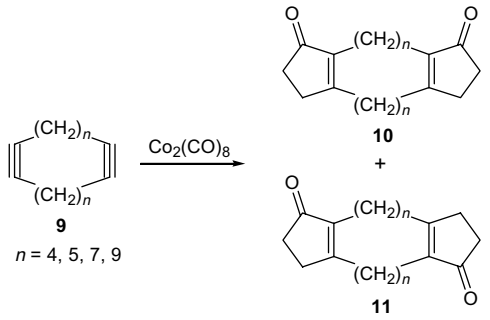


Scheme 3.

with Zn(Cu) couple, and the intramolecular coupling of the ester function of **5** with one of the ketone functions took place by slow addition of **5** to a heated DME solution of the low-valent titanium. The yield of **3** was a modest 18%,[13] but the saving in steps makes this route an attractive alternative to the original sequence.

A number of 2-aryl-1,3-cyclopentanedione compounds and some of their simple derivatives, for example **6** and **7**, have herbicidal and acaricidal activities.[14] These compounds can be produced in excellent yield by geminal acylation of the acetal of the aryl aldehyde (Scheme 3). The bicyclic bis(trimethylsilyloxy)cyclobutene derivative **8** was made via the acyloin reaction of diethyl (*cis*)-1,2-cyclohexanedicarboxylate by following the same procedure as for **1**.[2] In the presence of $BF_3{\cdot}Et_2O$, **8** and the diethyl acetal of 2,4-dimethylbenzaldehyde provided the sparingly soluble, geminally acylated product **6** directly, without the isolation of the cyclobutanone intermediate. Concomitant rearrangement of the cyclobutanone had been observed in the reactions of the acetals of other aromatic aldehydes.[9]

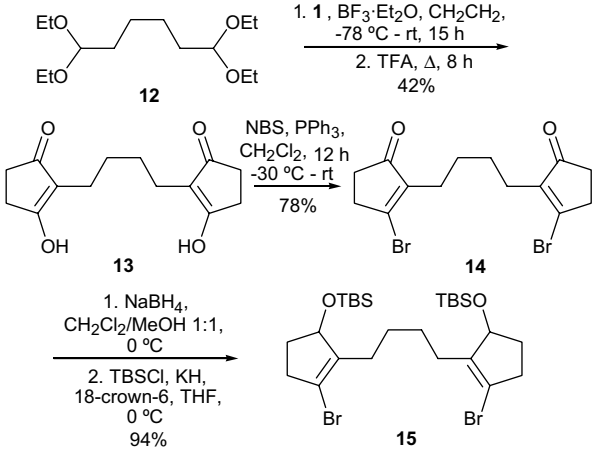
Carbocyclic [5.*X*.5] ring-systems with *X* larger than 8 are fairly rare. Jatrophatrione and citlalitrione are examples of diterpenes with [5.9.5] ring-systems.[15] These have been synthesized by Paquette and co-workers[16] by a route that initially provided the nine-membered ring via an anionic oxy-Cope reaction, but an unstoppable subsequent reaction annulated across the nine-membered ring. This necessitated cleavage of this unwanted bond by a Grob fragmentation. Exhaustive hydrogenation of doubly bridged ferrocenes gave saturated hydrocarbons with [5.10.5] and [5.12.5] ring-systems.[17] Carbocyclic [5.10.5] ring-systems have been prepared in moderate yield by intramolecular cyclization of bis(enones) mediated by Yb metal.[18] Double Pauson–Khand reactions of cyclic diynes **9** led to the formation of carbocyclic [5.*X*.5] diketones **10** and **11** in a ratio of 1:1, with $X = 12$, 14, 18 and 22 (Scheme 4). The yield of **10** plus **11** for $X = 14$ was 16% using DMSO as the promoter,[19] but addition of both DMSO and of *n*-butylmethyl sulfide to the reaction medium resulted in yields of 26–48%.[20]



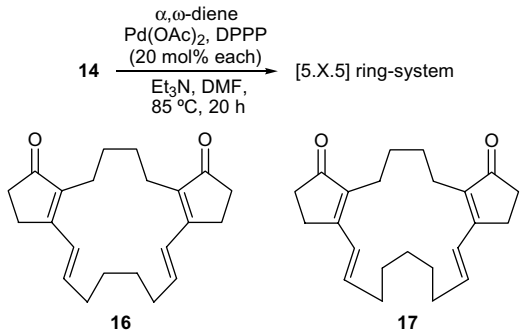
Scheme 4.

We considered using geminal acylation to form two 1,3-cyclopentanedione rings from a dialdehyde, and then addition of a second tether could form the central ring of a carbocyclic [5.*X*.5] diketone that is analogous to **10** without the production on the diketone analogous to **11**. Diacetal **12** of hexanedial and **1** reacted in the presence of $BF_3{\cdot}Et_2O$ to provide, after treatment with trifluoroacetic acid, the doubly geminally acylated product **13** in 42% yield (Scheme 5). The yield reflects, in part, the poor solubility of **13** in organic solvents.[9] Treatment of **13** with NBS and PPh_3[21] gave dibromide **14**. None of the desired tricyclic [5.12.5] dione was produced when **14** was exposed to the double-Grignard reagent derived from 1,4-dibromobutane, and **14** was unchanged after exposure to the bis-cuprate produced from the same dibromide. Reduction of **14** and silylation of the alcohols gave **15** as a mixture of diastereomers. Bromine–lithium exchange took place when *tert*-butyllithium was added to **15** in diethyl ether, but the organometallic would not add to the carbonyls of hexanedial, ethyl formate, or triphosgene.

Dibromide **14** did react readily with 1.5 equiv of 1,7-octadiene and with 1.5 equiv of 1,8-nonadiene under Heck conditions to afford [5.16.5] tetraenedione **16** and [5.17.5] tetraenedione **17** in yields of 72% and 79%, respectively (Scheme 6). In contrast, when 1.3 equiv of 2-methyl-1,5-hexadiene was employed, none of the [5.14.5] tetraenedione was detected, but the double



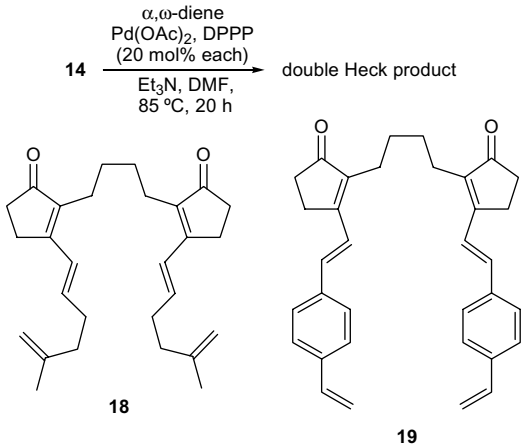
Scheme 5.



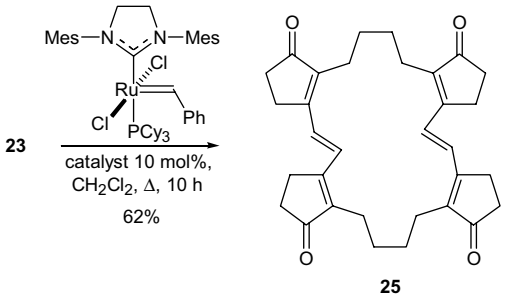
Scheme 6.

intermolecular Heck product **18** was isolated in 45% yield (based on **14**). In a similar way, under the Heck conditions 1.5 equiv of 1,4-divinylbenzene led only to the formation of the double intermolecular addition product, **19**, in 54% yield (based on **14**) (Scheme 7).

In an effort to form the [5.9.5] ring-system from **14** by a strategy of sequential Heck reactions onto the same alkene, a procedure was followed that had been successful with aryl bromides.[22] In the presence of $Pd(OAc)_2$, *n*-Bu_4NBr, sodium acetate and 1.3 equiv of ethyl acrylate in refluxing toluene, **14** gave 67% (based on ethyl acrylate) of the double intermolecular Heck product **20** along with a small amount of the singly reacted product **21**. None of the tricyclic compounds was detected, and resubjecting **21** to the Heck conditions did not lead to any tricyclic product. Under similar conditions, and also under the conditions used to prepare **16** and **17**, sometimes in the presence of Ag_2SO_4,[23] many attempts to form a tricyclic product with styrene led to the formation of the double intermolecular Heck product **22**. In addition, the reaction with ethyl acrylate was attempted in an ionic liquid with the Pd catalyst developed by Calò,[24] but the only product was **21** in 50% yield. A solution of compound **14**, $Pd(OAc)_2$, PPh_3 and triethylamine in acetonitrile was heated under reflux for 40 h under ethene (just over 1 atm). The double-Heck product **23** and the mono-Heck product **24** were obtained in yields of 29% and 47%, respectively. Resubjecting

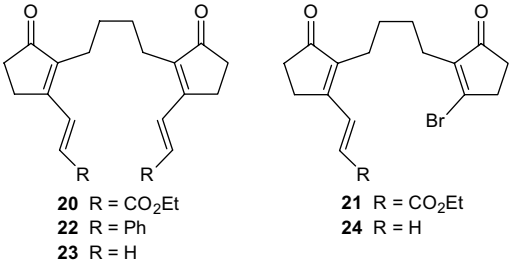


Scheme 7.



Scheme 8.

24 to Heck conditions did not give any tricyclic product. In summary, double Heck reactions are viable for the synthesis of [5.*X*.5] ring-systems from **14** when *X* is large and the reacting α,ω-diene is flexible and minimally substituted, but double Heck reactions onto the same alkene fail.



When **23** was heated with a catalytic amount of Grubbs' 'second generation' catalyst,[25] a cyclized product was produced smoothly, but mass spectrometry revealed that it was not a tricyclic [5.10.5] product, but the interesting pentacyclic compound **25**, the result of an initial bimolecular metathesis followed by ring-closing metathesis (Scheme 8). The *E*-geometry of the double bonds was evident from the coupling constant of 16.7 Hz, as determined by a coupled HSQC NMR experiment.[26]

Acknowledgement

We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Supplementary data

Characterization data for **3**, **6**, **7**, **13**–**25**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.089.

References and notes

1. Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759–1773.
2. Bloomfield, J. J.; Nelke, J. M. In *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 167–172.
3. (a) Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369–4372; (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804–811.

4. Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311–1318.
5. Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485–1491.
6. (a) Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722–8729; (b) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352–1355; (c) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708–5710.
7. Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1989**, *30*, 1021–1024.
8. Blanchard, A. N.; Burnell, D. J. *Tetrahedron Lett.* **2001**, *42*, 4779–4781.
9. Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356–359.
10. (a) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835–3838; (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816–819; (c) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. Fr.* **1993**, *130*, 447–449; (d) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104–110; (e) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921–9926; (f) Liu, P.-Y.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1183–1184; (g) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337–344; (h) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345–352; (i) Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3295–3304; (j) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335–7347; (k) Liu, P.-Y.; Wu, Y.-J.; Burnell, D. J. *Can. J. Chem.* **1997**, *75*, 656–664; (l) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1998**, 1755–1756; (m) Elliott, C. E.; Miller, D. O.; Burnell, D. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 217–226; (n) Chavan, S. P.; Kharul, R. K.; Kale, R. R.; Khobragade, D. A. *Tetrahedron* **2003**, *59*, 2737–2741; (o) Thornton, P. D.; Burnell, D. J. *Org. Lett.* **2006**, *8*, 3195–3199; (p) Joo, J. M.; Yuan, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 14818–14819.
11. Mehta, G.; Acharyulu, P. V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2759–2760.
12. McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748–3749.
13. The following procedures gave even lower yields: (a) McMurry, J. E.; Fleming, M. P. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709; (b) Newkome, G. R.; Roper, J. M. *J. Org. Chem.* **1979**, *44*, 502–505; (c) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991–6010; (d) Talukdar, S.; Nayak, S. K.; Banerji, A. J. *Org. Chem.* **1998**, *63*, 4925–4929, The mono-acetal of **5**, made with 1,2-ethanediol, underwent coupling using the conditions outlined in Scheme 2 to give the cyclized product in 12% yield.
14. (a) Wheeler, T. N. U.S. Patent 4283348, 1981; (b) Wheeler, T. N. U.S. Patent 4338122, 1982; (c) Wheeler, T. N. U.S. Patent 4436666, 1984; (d) Wheeler, T. N. U.S. Patent 4551547, 1985; (e) Fischer, R.; Dumas, J.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U.; Santel, H.-J.; Dollinger, M.; Turberg, A.; Mencke, N. U.S. Patent 5808135, 1998.
15. (a) Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Beavers, W. A.; Cutler, R. S. *J. Org. Chem.* **1976**, *41*, 1855–1857; (b) Villarreal, A. M.; Dominguez, X. A.; Williams, H. J.; Scott, A. I.; Reibenspies, J. *J. Nat. Prod.* **1988**, *51*, 749–753.
16. (a) Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L.-Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244–3254; (b) Paquette, L. A.; Yang, J.; Long, Y. O. *J. Am. Chem. Soc.* **2002**, *124*, 6542–6543; (c) Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567–1574.
17. Hillman, M.; Gordon, B.; Dudek, N.; Fajer, R.; Fujita, E.; Gaffney, J.; Jones, P.; Weiss, A. J.; Takagi, S. *J. Organomet. Chem.* **1980**, *194*, 229–256.
18. Taniguchi, Y.; Kusudo, T.; Beppu, F.; Makioka, Y.; Takaki, K.; Fujiwara, Y. *Nippon Kagaku Kaishi* **1994**, 62–67.
19. Rausch, B. J.; Gleiter, R. *Tetrahedron Lett.* **2001**, *42*, 1651–1653.
20. Gleiter, R.; Schulte, J. H.; Werz, D. B. *Eur. J. Org. Chem.* **2004**, 4077–4081.
21. Prashad, M.; Liu, Y.; Mak, X. Y.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002**, *43*, 8559–8562.
22. Yao, G.; Steliou, K. *Org. Lett.* **2002**, *4*, 485–488.
23. (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953–1954; (b) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371–382; (c) Miyazaki, F.; Uotsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073–13078.
24. Calò, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A. *Tetrahedron* **2001**, *57*, 6071–6077.
25. Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
26. Reynolds, W. F.; McLean, S.; Tay, L.-L.; Yu, M.; Enriquez, R. G.; Estwick, D. M.; Pascoe, K. O. *Magn. Reson. Chem.* **1997**, *35*, 455–462.