Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2459–2461

TETRAHEDRON LETTERS

Synthesis of functionalized bicyclo[3.2.1]octan-6-ones for diterpenoids: allylsilane directed Pummerer reaction: insertion reactions of diazoketones

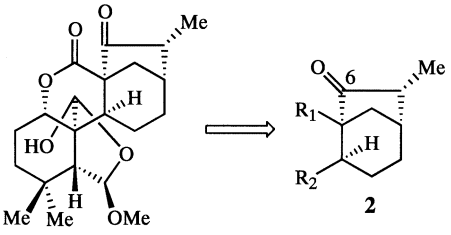
Philip Magnus,* Trevor Rainey and Vince Lynch†

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712, USA

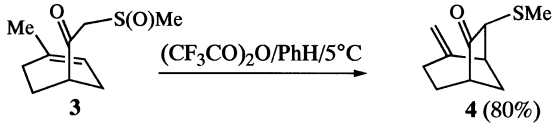
Received 20 December 2002; revised 31 January 2003; accepted 4 February 2003

Abstract—The sulfide **5** underwent Pummerer cyclization to give **6**, whereas the allyl silane analog **10** produced the bicyclo[3.2.1]octanones **11** and **11a**. Extension of this methodology to **15** resulted in **16** without the necessity for allyl silane activation. The intermediate diazoketone **14** on treatment with $BF_3{\cdot}OEt_2$ gave **17**, **18** and **19**, whereas the saturated adduct **22** on treatment with $Rh_2(OAc)_4$ gave **23**. © 2003 Elsevier Science Ltd. All rights reserved.

As part of a research program directed towards the synthesis of complex diterpenoids such as irroratin **1**[1] we required a method for the construction of functionalized bicyclo[3.2.1]octan-6-ones **2** (Eq. (1)). While the Pummerer reaction has been used to convert **3** into **4**,[2] it is notable that only the *exo*-methylene isomer was formed, and as a corollary, the methyl group in **3** may be mechanistically necessary for the formation of bicyclo[3.2.1]octanone **4** (Eq. (2)). Consequently, we initially decided to examine the prototype Pummerer reaction depicted in Scheme 1 to probe this conjecture.



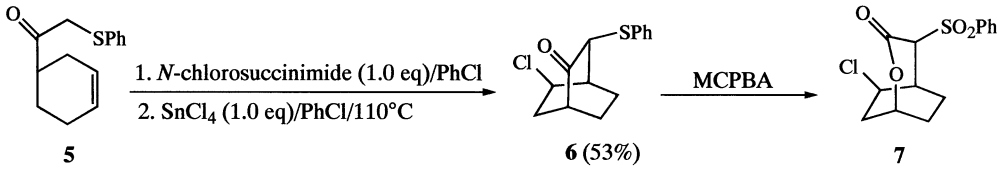
1, Irroratin **2** (1)



3 **4** (80%) (2)

Treatment of **5** with *N*-chlorosuccinimide in chlorobenzene followed by stannic tetrachloride and heating the mixture to 110°C gave **6** (ν_{max} 1726 cm^{-1}, indicated a cyclohexanone rather than cyclopentanone). The sulfoxide version of the Pummerer reaction on **5** (as in Eq. (2)) gave an intractable mixture. The structure of **6**[3] was confirmed by treatment with excess *m*-chloroperoxybenzoic acid to give **7** whose structure was established by X-ray crystallography.

To examine the allylic silane directed version of the above Pummerer reaction (Scheme 1) **8**[4] was converted into **9**,[5] and treated with $PhS(O)CH_2Li$ in THF to give **10**, Scheme 2. Exposure of **10** to the standard Pummerer reaction conditions of $(CF_3CO)_2O$/PhCl at 0°C and warming to 130°C resulted in **11** (55%, ν_{max} 1747



5 **6** (53%) **7**

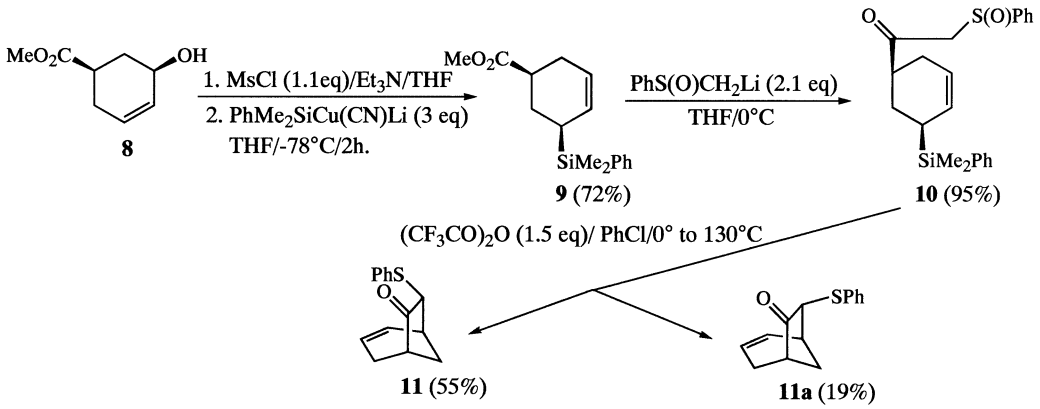
Scheme 1.

Keywords: bicyclo[3.2.1]octanones; Pummerer reaction; allylic silanes; diazoketones.

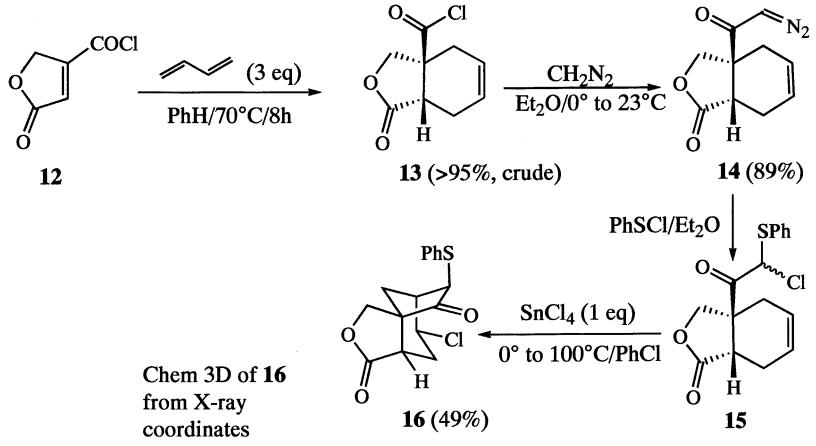
* Corresponding author.

† Author for inquiries concerning the X-ray data.

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)00336-8



Scheme 2.



Scheme 3.

cm^{-1}, indicated a cyclopentanone rather than cyclohexanone) and the phenylthio epimer **11a** (19%, ν_{max} 1742 cm^{-1}).[6]

Aconyl chloride **12**[7] reacted with 1,3-butadiene to give **13**.[8] The most direct way to convert **13** into a suitable precursor to an intramolecular Pummerer reaction (as in Scheme 2) was to treat **13** with diazomethane to give **14**, followed by phenyl sulfenyl chloride, resulting in **15**, Scheme 3.[9] We initially opted to examine the Pummerer reaction without the benefit of allylic silane assistance since the substrate **15** was readily made and would provide a logical comparison with **5** (Scheme 1). Furthermore, while the allylic silane directed Pummerer reaction on the simple model (Scheme 2) changed the selectivity from a bicyclo[2.2.2]octane to a bicyclo[3.2.1]octane, the introduction of the allylic silane functionality into **15** (or precursors) would add a substantial number of steps to the synthesis. In the event, treatment of **15** with stannic tetrachloride and heating the mixture to 100°C gave **16** (49%, structure confirmed by X-ray) (Fig. 1). We could not detect any isomeric bicyclo[2.2.2]octanones.

Since the diazoketone **14** is the precursor to **16** we also examined its reactivity with respect to the formation of bicyclo[3.2.1]octan-6-ones. Treatment of **14** with $BF_3{\cdot}OEt_2$ in dichloromethane at 0–23°C gave **17** (13%), **18** (19%) and **19** (23%) (Scheme 4). Interestingly, while treatment of **14** with $Rh_2(OAc)_4$ (2 mol%) gave the cyclopropane **20** (X-ray) in nearly quantitative yield, attempts to rearrange **20** into **17**, **18** and **19** by exposure to $BF_3{\cdot}OEt_2$ even in 1,2-dichloroethane heated at reflux failed.[10]

To examine the formation of the bicyclo[3.2.1]octanone system via a C–H insertion process[11] we hydrolyzed **13** to give **21** which was converted into **22** by standard reactions, Scheme 5. Exposure of **22** to $Rh_2(OAc)_4$ (2 mol%) gave the required insertion product **23** (67%),[12] along with about 10–15% of a by-product that is most likely a cyclobutanone (^{13}C 210 ppm).

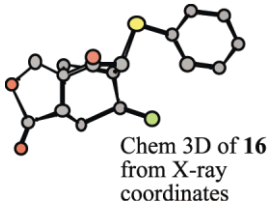
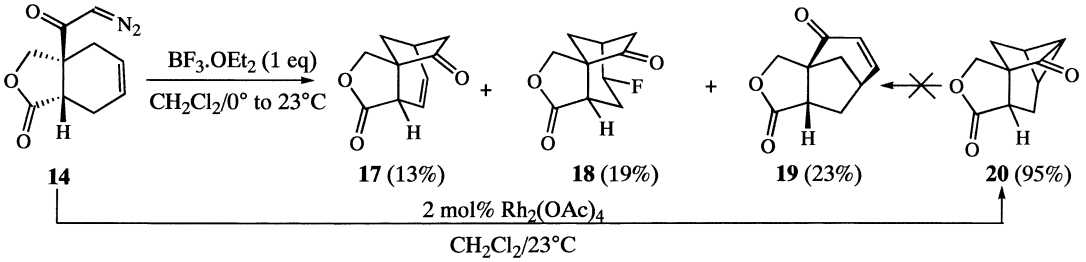
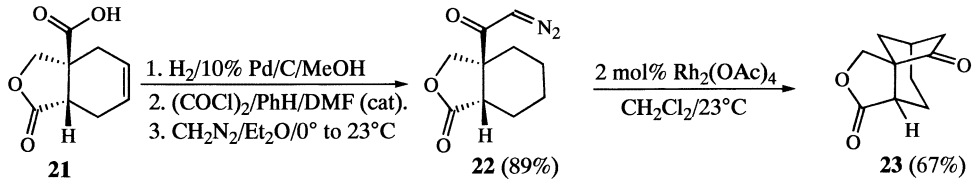


Figure 1.



Scheme 4.



Scheme 5.

The combination of the highly oxidized isoprene unit, namely aconyl chloride in [2+4] cycloaddition chemistry to give **13**, and its elaboration via a diazoketone C–H insertion reaction to give **23**, provides a very direct route to suitably functionalized bicyclo[3.2.1]octan-6-ones which may have potential for the synthesis of diterpenes such as **1** and related structures.

Acknowledgements

The Robert A. Welch Foundation, Merck Research Laboratories and Novartis are thanked for their support of this research.

References

1. Sun, H.-D.; Qiu, S.-X.; Lobkovsky, E. B.; Lin, L.-Z.; Farnsworth, N. R.; Clardy, J.; Fong, H. H. S. *Tetrahedron* **2001**, *57*, 65–70.
2. Mander, L. N.; Mundill, P. H. C. *Synthesis* **1981**, 620.
3. (a) Mi, B.; Maleczka, R. E. *Tetrahedron Lett.* **1999**, *40*, 2053; (b) King, J. F.; Rathore, R.; Guo, Z.; Li, M.; Payne, N. C. *J. Am. Chem. Soc.* **2000**, *122*, 10308.
4. (a) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230; (b) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378; (c) Nicolaou, K. C.; Sietz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884; (d) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854; (e) Martin, S. F.; Dappen, M. S.; Dupré, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209; (f) Smith, A. B.; Hale, K. J.; Laakso, L. M.; Chen, K.; Riéra, A. *Tetrahedron Lett.* **1989**, *30*, 6963; (g) Trost, B. M.; Kondo, Y. *Tetrahedron Lett.* **1991**, *32*, 1613; (h) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
5. Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415.
6. **11**. R_f 0.16 (10% EtOAc/hexanes.) IR (neat) 1747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.46 (2H, m), 7.31–7.19 (3H, m), 6.05–5.99 (1H, m), 5.68–5.63 (1H, m), 3.96 (1H, d, $J=5.9$ Hz), 3.03–2.97 (1H, m), 2.75 (1H, br s), 2.52–2.43 (1H, m), 2.33–2.25 (1H, m), 2.12–2.10 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 135.3, 131.1, 130.4, 128.6, 126.5, 126.2, 65.0, 44.2, 36.7, 32.8, 31.4 ppm. HRMS calcd for $C_{14}H_{15}OS$ (MH^+) 231.0844. Found 231.0851.
7. Cambell, N. R.; Hunt, J. H. *J. Chem. Soc.* **1947**, *1*, 1176.
8. Susuki, Y.; Ohara, A.; Sugaya, K.; Takao, K.; Tadano, K. *Tetrahedron* **2001**, *57*, 7291.
9. (a) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1983**, *24*, 117; (b) Weyland, F.; Bestmann, H. J. *Z. Naturforsch.* **1955**, *10b*, 269; (c) Aszodi, J.; Chantot, J.-F.; Collard, J.; Teutsch, G. *Heterocycles* **1989**, *28*, 1061.
10. Erman, W. F.; Stone, L. C. *J. Am. Chem. Soc.* **1971**, *93*, 2821.
11. (a) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds. Carbon–carbon bond formation by C–H insertion. Pergamon Press, 1991; Vol. 3, p. 1045; (b) Doyle, P. M.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. From Cyclopropanes to Ylides*; J. Wiley & Sons, 1998.
12. **23**. Mp 103–104°C (EtOAc/hexanes.), R_f 0.31 (1:1 hexanes:EtOAc.) IR (thin film) 1772, 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (1H, d, $J=9.5$ Hz), 4.00 (1H, d, $J=9.5$ Hz), 2.68–2.62 (1H, m), 2.53 (1H, t, $J=8.3$ Hz), 2.44–2.35 (1H, m), 2.20–2.10 (2H, m), 2.09–1.94 (1H, m), 1.92–1.82 (2H, m), 1.79–1.72 (1H, m), 1.49–1.39 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 176.0, 69.6, 54.2, 44.8, 43.6, 32.8, 26.7, 16.7 ppm. HRMS calcd for $C_{10}H_{13}O_3$ (MH^+) 181.0865. Found 181.0856. Derived ethylene ketal. IR (neat) 1778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.02–3.85 (6H, m), 2.84 (1H, dd, $J=3.5$, 8.8 Hz), 2.26–2.22 (1H, m), 2.10–2.02 (1H, m), 1.95–1.78 (3H, m), 1.67 (1H, dd, $J=1.7$, 14.4 Hz), 1.60–1.44 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 114.9, 70.3, 65.2, 64.2, 52.0, 42.2, 41.3, 36.0, 29.1, 28.6, 15.5 ppm. HRMS calcd for $C_{12}H_{17}O_4$ (MH^+) 225.1127. Found 225.1134.