Pergamon

Tetrahedron Letters 42 (2001) 1135–1138

TETRAHEDRON LETTERS

1,3- versus 1,4-Asymmetric induction in Mukaiyama–Michael additions of optically active ketene acetals to 2-methylcyclopent-2-en-1-one: a remarkable inversion of facial selectivity

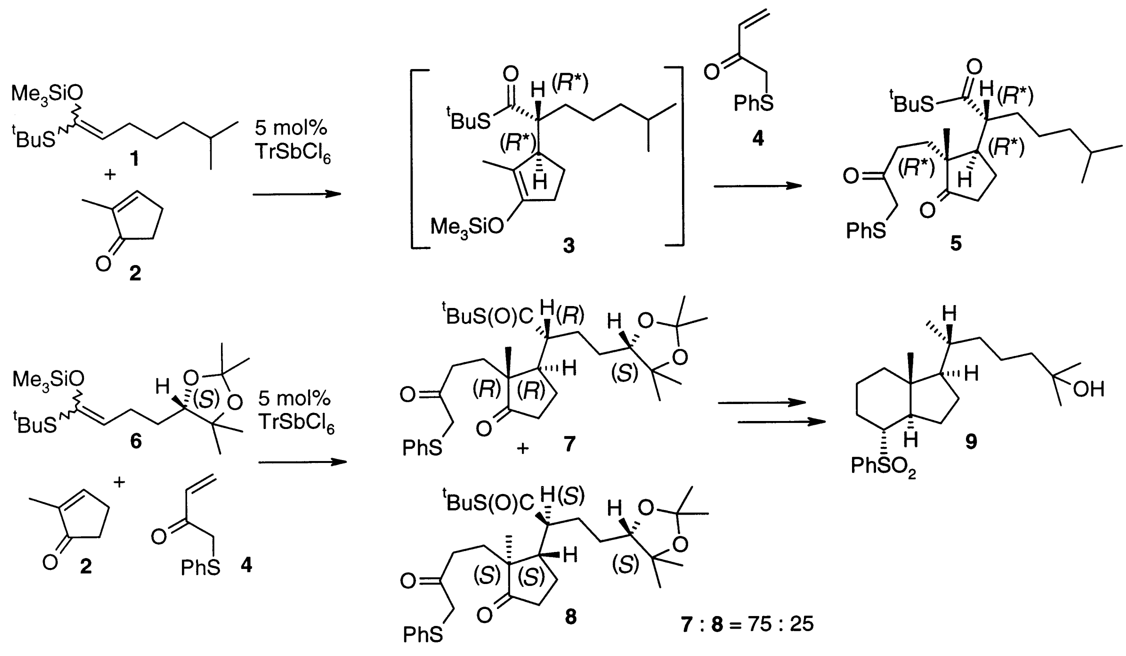
Evgueni Gorobets, Zofia Urbanczyk-Lipkowska, Viatcheslav Stepanenko and Jerzy Wicha*

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44, 01-224 Warsaw 48, Poland

Received 22 September 2000; revised 13 November 2000; accepted 22 November 2000

Abstract—$TrSbCl_6$-catalyzed addition of selected optically active ketene acetals to 2-methylcyclopent-2-en-1-one for steroid synthesis is described. Inversion of facial selectivity in 1,3- and 1,4-asymmetric induction was observed. © 2001 Elsevier Science Ltd. All rights reserved.

Trityl salt-catalyzed conjugate addition reactions of prostereogenic silylated ketene acetals to prostereogenic α,β-unsaturated ketones is known to provide the corresponding adducts with high diastereoselectivity.[1–3] Asymmetric variations of the reaction include: (a) the conjugate addition of prochiral ketene acetals to opti-

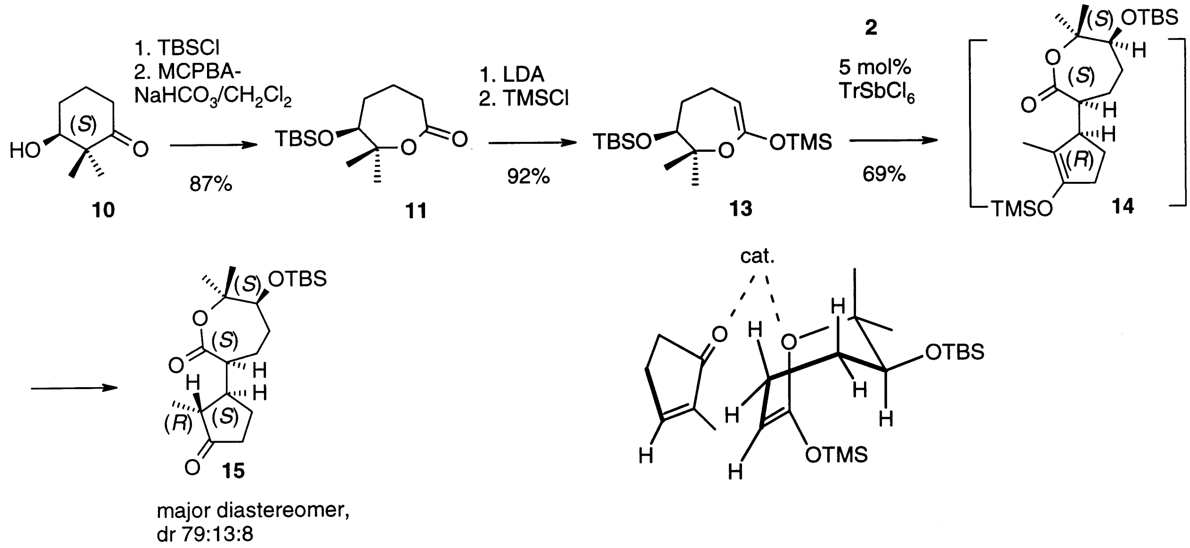


Scheme 1. Diastereoselectivity in Mukaiyama–Michael conjugate addition with prostereogenic components and optically active ketene acetal **8**.

Keywords: Mukaiyama–Michael reaction; asymmetric induction; Sharpless dihydroxylation; steroids.

* Corresponding author. E-mail: jwicha@icho.edu.pl

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)02166-3



Scheme 2. Preparation of cyclic ketene acetal **14** and its reaction with 2-methylcyclopent-2-en-1-one.

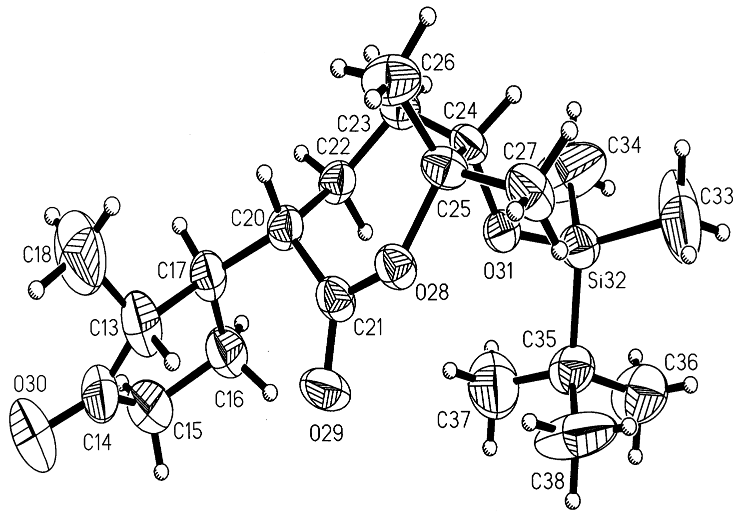


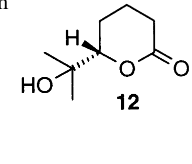
Figure 1. X-Ray structure of compound **15**.

cally active α,β-unsaturated ketones;[4,5] (b) the addition of optically active ketene acetals bearing a chiral auxiliary to prochiral α,β-unsaturated ketones;[6] and (c) the use of chiral catalysts.[7–10] The catalytic asymmetric Mukaiyama–Michael reaction has rarely been applied to natural product synthesis till now.[11]

We recently developed[12–14] a steroid synthesis based upon the trityl salt-catalyzed conjugate addition of ketene acetal **1** to methylcyclopentenone **2** followed by a second conjugate addition to the α,β-unsaturated ketone **4** (Scheme 1). The intermediate adduct **3** with *like* configuration at the newly formed chiral centers predominated (dr ca. 9:1). Conjugate addition of **3** and **4** was highly diastereoselective[15] affording racemic **5**. In designing an enantioselective approach to **5** and related intermediates we chose to use optically active derivatives of **1** easily accessible by Sharpless asymmetric dihydroxylation or by certain microbiological transformations. Indeed, the tandem conjugate addition reactions of optically active ketene acetal **6** and the Michael acceptors **2** and **4** occurred with a significant asymmetric induction to provide the desired diastereomer **7** as the major product[16] (**7**:**8** = 75:25, 55% yield). The intermediate **7** was eventually transformed into compound **9** which is a known intermediate in synthesis of vitamin D_3 congeners.[17,18]

In order to gain insight into the structural factors determining the asymmetric induction in the conjugated addition reaction, we examined the behavior of selected ketene acetals related to **6**. Hydroxyketone **10**, prepared by yeast reduction of 2,2-dimethylcyclohexa-1,3-dione,[19] was transformed into lactone **11** by silylation followed by Baeyer–Villiger oxidation† (Scheme 2).

† Oxidation of hydroxy ketone **10** with M-CPBA gave the product[16] which resisted reaction with TBSCl under the usual conditions. It was concluded that the Baeyer–Villiger oxidation was accompanied by rearrangement to give a tertiary carbinol **12**.



12

Ketene acetal[20] **13**, prepared from **11** in the usual way, was submitted to the reaction with enone **2** in the presence of $TrSbCl_6$, followed by hydrolysis to give three components (69% yield) in a ratio of 79:13:8 (by ^{1}H NMR). All our attempts to separate this mixture by chromatography failed. Fortunately, the major diastereomer **15** crystallized and was obtained in a pure form by recrystallization from pentane (51% yield from **13**). Its structure **15** was determined by a single crystal X-ray analysis (Fig. 1). The formation of **15** must involve the intermediate silyl enol ether **14** (17*R*,20*S*, steroid numbering) and, consequently, the Mukaiyama–Michael reaction occurred mainly in the *unlike* fashion. The new carbon–carbon bond was formed on the face of the seven-membered ring that bears the TBSO group, which suggests that chelation of the catalyst may involve the oxygen atom of this group. However, inspection of molecular models indicates that ketene acetal **13** enters the reaction in a boat conformation with the bulky *tert*-butyldimethylsilyl group in the pseudo equatorial position, as shown in Scheme 2. On this premise the cyclopentenone approached the electrophile on its *re* face with the methyl group oriented outside of the ring and the oxygen atoms of the reactants in a *syn* orientation.

Initial attempts to conduct in situ conjugate addition of silyl enol **14** to enone **4** showed that the reaction is slow and is accompanied by substantial decomposition of the enone. Since the relative configuration at C17 and C20 in **14** differs from that occurring in major natural sterols, attempts to find favorable conditions for its reaction with **4** were abandoned.

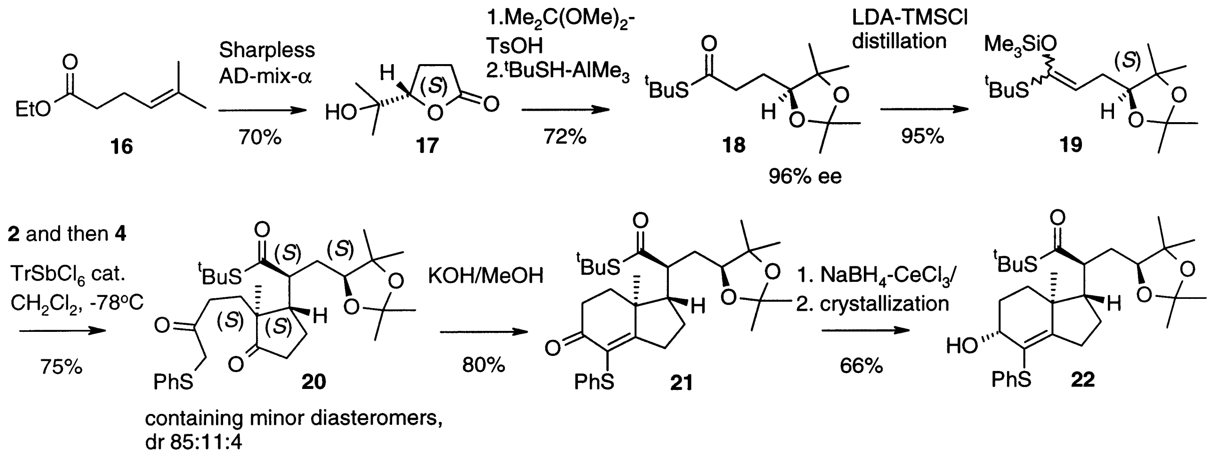
Compound **19** (Scheme 3) was the next objective in our asymmetric induction studies. Like ketene acetal **6**, it has an asymmetric carbon atom of (*S*)-configuration, which is incorporated into a dioxolane ring. However, in the ketene acetal **19** the asymmetric carbon atom is closer to the reaction site (1,3). Synthesis of **19** is presented in Scheme 3. Unsaturated ester **16** underwent Sharpless asymmetric dihydroxylation using AD-mix-α® to give hydroxy lactone **17** as the only product (70% yield after distillation). Treatment of **17** with 2,2-dimethoxypropane-TsOH and then with *tert*-BuSH and $AlMe_3$[21] afforded thioester **18** (72% yield, 96% ee by HPLC on a Chiralcel OD® column). The latter was transformed into ketene acetal **19** (E:Z = 85:15 by ^{1}H NMR) in the usual way.

The tandem reaction of **19** with Michael acceptors, **2** and **4** in the presence of the trityl catalyst, afforded an oily adduct consisting of three diastereomers in a ratio of 85:11:4 (75% yield). The diastereomers could not be separated by chromatography but it was found that annulation followed by the Luche reduction[22] afforded a crystalline material. The main component of the mixture isolated by crystallization from benzene was **22** according to single crystal X-ray analysis (Fig. 2). Consequently, the structures of major intermediates were identified as **20** and **21**, respectively.

Reaction of the ketene acetals **6**, **13** and **19** with methylcyclopentenone **2** occurs with different stereoselection. The cyclic reagent **13** gives the major adduct with *unlike* relative configuration at the newly formed stereogenic centers (17*R*,20*S*), whereas the linear ketene acetals **6** and **19**, both of (*S*)-configuration, afford products with *like* configuration at the newly generated stereogenic centers, in accord with the rule operating for prostereogenic ketene acetals. However, 1,4-asymmetric induction in **6** provides the major product with absolute configuration 17*R*,20*R* (75% of the diastereomer mixture), whereas 1,3-induction in **19** gives the major product with 17*S*,20*S* configuration (85% of the mixture). To the best of our knowledge, the observed change in the direction of remote asymmetric induction has no precedent in the literature.[23] Work to determine further structural requirements for remote asymmetric induction in the Mukaiyama–Michael reaction is now in progress.

Acknowledgements

We thank Professor Philip Kocienski for helpful discussions. Financial support from the State Committee for Scientific Research, Grant No. 3 T09A 134 18, is gratefully acknowledged.



Scheme 3. Preparation of ketene acetal **19** and its use in tandem Mukaiyama–Michael reaction.

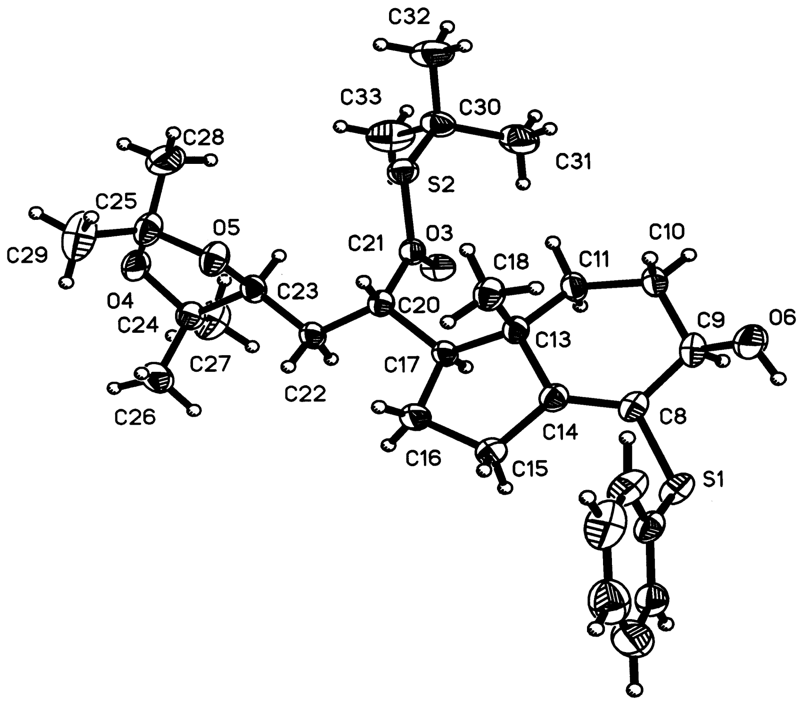


Figure 2. X-Ray structure of compound **22**.

References

1. Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223–1224.
2. Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1817–1820.
3. Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1991; Vol. 20, pp. 87–170.
4. Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *114*, 8349–8362.
5. Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279–280.
6. Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754–2760.
7. Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97–100.
8. Bernardi, A.; Colombo, G.; Scolastico, G. *Tetrahedron Lett.* **1996**, *37*, 8921–8924.
9. Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568–570.
10. Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865–868.
11. Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165–1170.
12. Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218–2223.
13. Michalak, K.; Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 7657–7658.
14. Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293–5298.
15. Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387–396.
16. Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1998**, *39*, 885–888.
17. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1290–1293.
18. Blakemore, P. R.; Grzywacz, P.; Kocienski, P. J.; Marczak, S.; Wicha, J. *Pol. J. Chem.* **1999**, *73*, 1209–1217.
19. Mori, K.; Mori, H. *Org. Synth.* **1990**, *68*, 56–62.
20. For some reactions of related cyclic ketene acetals, see: Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2117–2120.
21. Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960–3961.
22. Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601–602.
23. For representative references on remote asymmetric induction, see: Ho, T.-L. *Stereoselectivity in Synthesis*; Wiley-Interscience: New York, 1999, Chapter 4.