Pergamon

Tetrahedron Letters 43 (2002) 3633–3636

TETRAHEDRON
LETTERS

Synthetic study of bicyclo[5.2.1]dec-8-en-4-ones based on tandem anionic [1,3] and oxy-Cope rearrangements of 2-vinylbicyclo[3.2.1]oct-6-en-2-ols

Hiroki Hashimoto,[a] Toshihiro Jin,[a] Michinori Karikomi,[a] Katsura Seki,[b,]* Kazuo Haga[a] and Tadao Uyehara[a]

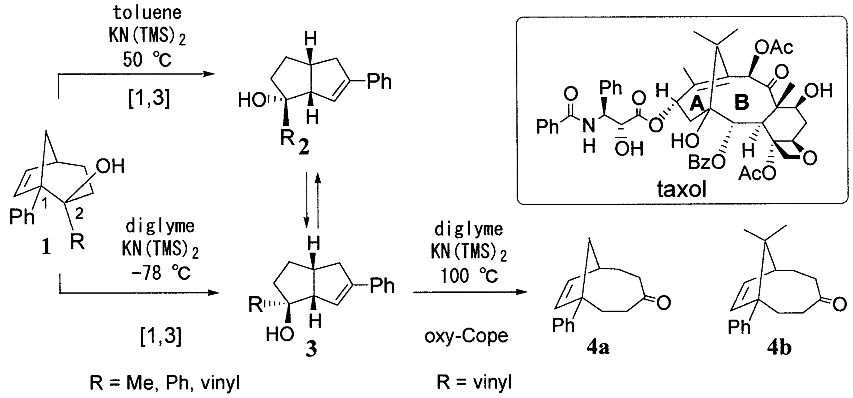
[a]*Department of Applied Chemistry, Faculty of Engineering, Utsunomiya University, Utsunomiya 321-8585, Japan*
[b]*Center for Instrumental Analysis, Utsunomiya University, Utsunomiya 321-8585, Japan*

Received 21 February 2002; revised 18 March 2002; accepted 29 March 2002

Abstract—An efficient one-pot synthesis of a 10,10-ethylenebicyclo[5.2.1]dec-8-en-4-one derivative, which can be considered as a synthetic intermediate for the taxane skeleton, has been achieved by tandem anionic [1,3] and oxy-Cope rearrangements of 2-vinylbicyclo[3.2.1] oct-6-en-2-ol. © 2002 Elsevier Science Ltd. All rights reserved.

Alkoxide-accelerated [1,3] sigmatropic rearrangements have rarely been investigated from either the mechanistic or synthetic point of view.[1,2] In the course of our studies on systematic construction of [*m*-*n*] fused-ring skeletons through anionic [1,3] rearrangement of bridged bicyclic compounds,[3] we have recently reported the reaction conditions in the stereoselective preparation of [5-5] fused-ring compounds, the so-called diquinanes **2** and **3**, from 1-phenylbicyclo[3.2.1]oct-6-en-2-ols **1**. As a special case of this reaction, 2-vinyl derivative **1a** gave a ring-expanded ketone **4a** in good yield through tandem [1,3] and [3,3], viz., oxy-Cope, rearrangements (Scheme 1).[4]

To our knowledge, such an efficient synthetic method for the bicyclo[5.2.1]decane system has hitherto not been reported.[5] This system would be easily converted into a bicyclo[5.3.1]undecane system,[5b,6] which corresponds to the A- and B-rings of the taxane skeleton,[7] by one-carbon expansion of its etheno-bridge. However, the taxane skeleton possesses a *gem*-dimethyl group on the methano-bridge. Thus, we attempted to



Scheme 1.

Keywords: taxane skeleton; bicyclic compounds; [1,3] rearrangement; oxy-Cope rearrangement.

* Corresponding author. E-mail: sekik@cc.utsunomiya-u.ac.jp

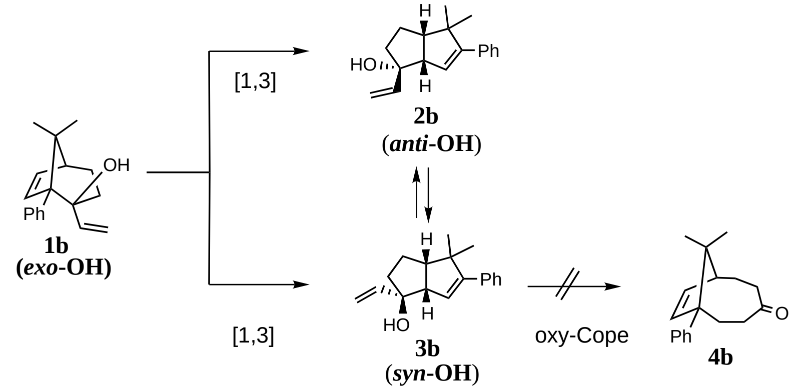
PII: S0040-4039(02)00648-2

develop a method for the construction of the bicyclo[5.2.1]decane system having the dimethylmethano-bridge. In this letter, we would like to report a unique strategy for the one-pot synthesis of a precursor of the taxane skeleton by employing a combination of anionic [1,3] and oxy-Cope rearrangements.

Substrates, 1-phenyl-2-vinylbicyclo[3.2.1]oct-6-en-2-ols **1b–d**,[†] were prepared by the Grignard reaction of the corresponding ketones and vinylmagnesium bromide.[2a,3b,4,8]

The sigmatropic rearrangements of **1b**, having a *gem*-dimethyl group on the methano-bridge in **1a**, and its related compounds (**2b**, **3b**) were first examined under the conditions as listed in Table 1 (see Scheme 2). The results of anionic [1,3] rearrangement of **1b** were similar to those[4] of **1a**; a reaction of **1b** using potassium bis(trimethylsilyl)amide [KN(TMS)$_2$] in toluene at 30°C gave **2b** in 78% yield (entry 1), while a similar treatment of **1b** in diglyme at −78°C afforded **3b** in 81% yield (entry 2). The conversion of **1b** to the corresponding ring-expanded ketone **4b** was, however, unsuccessful (entries 2 and 3).

The oxy-Cope rearrangement of the diquinqane **3b** also did not proceed at 120°C in diglyme, and a mixture of **2b** and **3b** was obtained accompanied with decomposition of the diquinanes (entry 5).

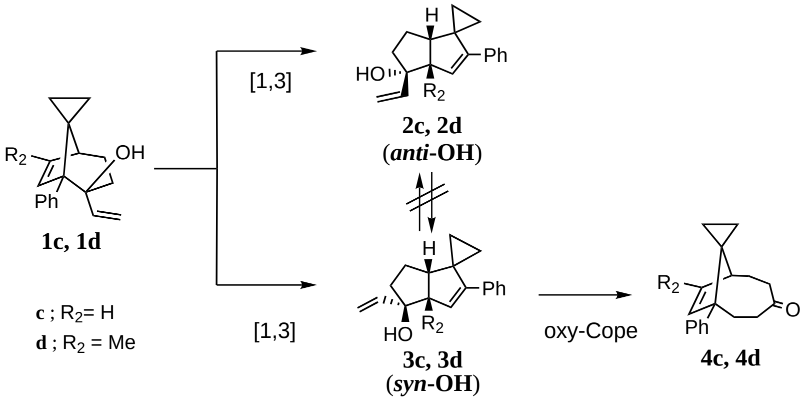


Scheme 2.

Table 1. Anionic [1,3] and oxy-Cope rearrangements of bicyclo[3.2.1]oct-6-en-2-ols[a]

Entry	Substrate	Solvent	Temp. (°C)/time (min)	Yield (%)		
				2b	**3b**	**4b**
1	**1b**	Toluene	30/600	78	–	–
2	**1b**	Diglyme	−78/15	17	81	–
3	**1b**	Diglyme	145/15	18	23	–
4	**2b**	Diglyme	145/15	25	22	–
5	**3b**	Diglyme	120/60	26	22	–

[a] Reaction was carried out using 3 equiv. of potassium bis(trimethylsilyl)amide under an argon atmosphere.



Scheme 3.

[†] All new compounds reported here exhibit satisfactory spectral characteristics including HRMS.

Table 2. Anionic [1,3] and oxy-Cope rearrangements of bicyclo[3.2.1]oct-6-en-2-ols[a]

Entry	Substrate	Solvent	Temp. (°C)/time (min)	Yield (%)		
				2	**3**	**4**
1	**1c**	Diglyme	−78/15	19 (**2c**)	60 (**3c**)	– (**4c**)
2	**1c**	Diglyme	50/120	34 (**2c**)	32 (**3c**)	24 (**4c**)
3	**1c**	Diglyme	100/60	40 (**2c**)	42 (**3c**)	Trace (**4c**)
4	**1d**	Diglyme	−40/30	– (**2d**)	61 (**3d**)	11 (**4d**)
5	**1d**	Diglyme	100/15	42 (**2d**)	– (**3d**)	38 (**4d**)
6	**1d**	Diglyme	−40/30→100/15	– (**2d**)	– (**3d**)	86 (**4d**)
7	**2c**	Diglyme	100/60	83 (**2c**)	– (**3c**)	– (**4c**)
8	**3c**	Diglyme	50/120	– (**2c**)	53 (**3c**)	13 (**4c**)
9	**2d**	Diglyme	100/15	65 (**2d**)	– (**3d**)	– (**4d**)
10	**3d**	Diglyme	100/15	– (**2d**)	– (**3d**)	81 (**4d**)

[a] Reaction was carried out using 3 equiv. of potassium bis(trimethylsilyl)amide under an argon atmosphere.

The low reactivity of the diquinane **3b** could be explained by steric repulsion between the *gem*-dimethyl group and the vinyl group. That is, the bulky substituents on the methano-bridge must prevent the approach of the vinyl group to the vinylene group for the formation of **4b**, as shown by **3b** in Fig. 1.

We then employed **1c**, possessing a less hindered ethylene group instead of the *gem*-dimethyl group, as a substrate, because the ethylene group can be converted to a *gem*-dimethyl group by reduction.[9] Treatment of **1c** with $KN(TMS)_2$ in diglyme at −78°C gave two diquinanes **2c** and **3c** (entry 1 in Table 2) (see Scheme 3), while the reaction of **1c** at 50°C afforded the ketone **4c** in 24% yield together with **2c** and **3c** (entry 2). However, the yield of **4c** was not improved even at elevated temperature (entry 3). The result of the anionic rearrangement of **2c** was different from that of **2b** (see entry 4 in Table 1); not only the formation of **4c**, but also the interconversion from **2c** to **3c** was not observed under the same treatment of **2c** at 100°C (entry 7). On the other hand, the treatment of **3c** at 50°C gave **4c** only in 13% yield (entry 8).

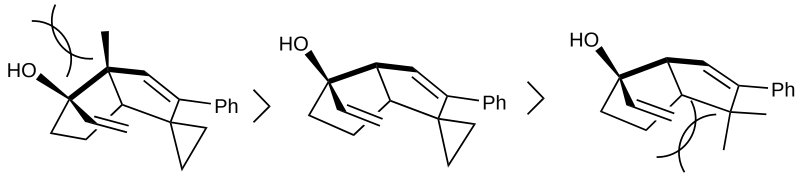
In the case of **1d**, which possesses a methyl group on the vinylene carbon, the desired ketone **4d** was obtained in 38% yield along with almost equal amounts of **2d** (entry 5). Under the same conditions, the resulting diquinane **2d** did not give **3d** as well as **4d** (entry 9), while the same treatment of its diastereoisomer **3d** gave **4d** in 81% yield (entry 10). These results suggest that the ring-expanded ketone **4d** must be formed through the oxy-Cope process of the alcoholate of **3d**, which would take a suitable conformation for the oxy-Cope rearrangement by the steric repulsion between the methyl group and the alkoxy anion in its alcoholate (Fig. 1). As shown in Fig. 1, the reactivities of the diquinanes on the oxy-Cope rearrangement increase in the following order: **3d**>**3c**>**3b**.

The reaction conditions for the one-pot synthesis of **4d** from **1d** were finally examined and the desired ketone **4d** was efficiently obtained as follows: The substrate **1d** was treated at −40°C in diglyme during the initial 30 min to give **3d** and the solution was then heated at 100°C for 15 min to afford the desired ketone **4d** in 86% yield (entry 6).

In conclusion, we have developed a practical method for the construction of a bicyclo[5.2.1]decane system having the ethylene group on its methano-bridge, which can be considered as a synthetic intermediate for the taxane skeleton,[10] by using anionic [1,3] rearrangement and subsequent oxy-Cope rearrangement.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, of the Japanese Government (12490004) and Sasakawa Scientific Research Grant from the Japan Science Society.

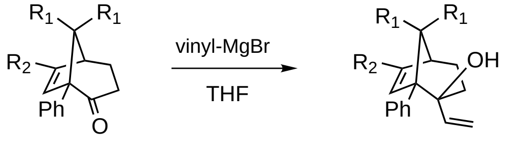


3d **3c** **3b**

Figure 1. The reactivities of the diquinanes on the oxy-Cope rearrangement.

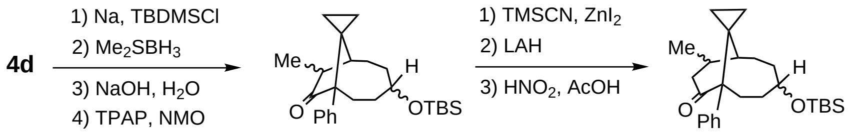
References

1. For the reviews on anionic rearrangement, see: (a) Paquette, L. A. *Synlett* **1990**, 67–73; (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626; (c) Paquette, L. A. *Stud. Nat. Prod. Chem.* **1996**, *18*, 3–42; (d) Paquette, L. A. *Tetrahedron* **1997**, *41*, 13971–14020.
2. For the synthesis of natural products, see: (a) Uyehara, T.; Sato, Y.; Ishizuka, H.; Sakiyama, Y.; Ueno, M.; Sato, T. *Tetrahedron Lett.* **2000**, *41*, 1939–1942; (b) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, C. R. *J. Org. Chem.* **1998**, *63*, 6905–6913; (c) Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845–850.
3. (a) Uyehara, T.; Inayama, T.; Ueno, M.; Sato, T. *Chem. Lett.* **1996**, 389–390; (b) Seki, K.; Kiyokawa, W.; Hashimoto, H.; Uyehara, T.; Ueno, M.; Sato, T. *Chem. Lett.* **1996**, 1035–1036.
4. Hashimoto, H.; Seki, K.; Kiyokawa, W.; Ueno, M.; Sato, T.; Uyehara, T. *Tetrahedron Lett.* **1999**, *40*, 511–514.
5. For reviews on the bicyclo[5.2.1]decane system, see: (a) Verma, S. K.; Nguyen, Q. H.; MacDougall, J. M.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, *65*, 3379–3386; (b) Ghosh, S.; Sarkar, S.; Saha, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2281–2286.
6. For examples of homologation, see: Collado, I.; Ezquerra, J.; Mateo, A. I.; Rubio, A. *J. Org. Chem.* **1998**, *63*, 1995–2001; Ghosh, S.; Sarkar, S.; Saha, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1587–1591; Smith, P. A. S.; Bear, D. R. *Org. React.* **1960**, *11*, 157–189.
7. For total synthesis of taxol, see: (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Sindou, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598; (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634.
8. Uyehara, T.; Inayama, T.; Furuta, T.; Kato, T.; Yamamoto, Y.; Ueno, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1727–1735. The substrates **1b–d** were obtained as a single isomer from the corresponding ketones **5b–d**, which were derived from 1-methoxybicyclo[2.2.2]oct-5-en-2-one and its related compounds.
9. (a) Stahl, K.-J.; Hertzsch, W.; Musso, H. *Liebigs Ann. Chem.* **1985**, 1474–1484; (b) Liu, H. J.; Kulkarni, M. G. *Tetrahedron Lett.* **1985**, *26*, 4847–4850; (c) Leonard, J.; Bennett, L.; Mahmood, A. *Tetrahedron Lett.* **1999**, *40*, 3965–3968.
10. Bicyclo[5.3.1]undecane derivative **6** having a taxane skeleton was then synthesized by Tiffeneau–Demjanov rearrangement of **5** as follows.



5b-d **1b-d**

b ; R_1 = Me, R_2 = H
c ; R_1-R_1 = CH_2-CH_2, R_2 = H
d ; R_1-R_1 = CH_2-CH_2, R_2 = Me



5 **6**