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Cope Rearrangement of $\Delta^{3,8}$-Taxane Tricarbocycles: Remarkable Solvent Effect on Product Distribution.

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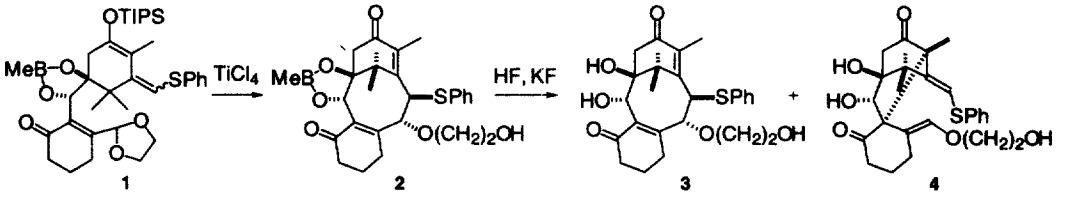
Abstract: Cope rearrangement of the taxane-like tricyclic compounds having a 1,5-diene moiety readily takes place to give novel spirocyclic compounds. This transformation is found to be reversible and the product distribution is greatly dependent on the solvent polarity: the reactions in chloroform afford the taxane-like tricarbocycles, while those in methanol give the spirocyclic compounds exclusively.

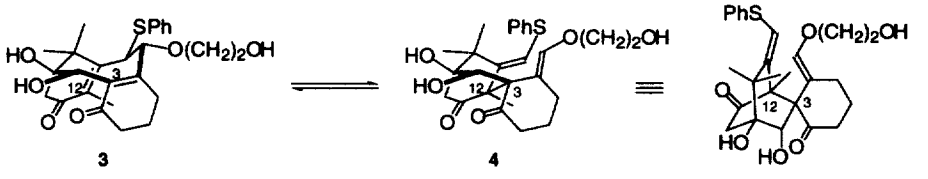
Keywords: rearrangements; dienes; solvents and solvent effects; taxoids

In connection with our program for the total synthesis of taxane diterpenoids such as taxusin [1] and taxol [2], we have already developed an efficient method for the construction of the taxane tricyclic skeleton by means of the intramolecular aldol-type 8-membered B-ring cyclization [3]. One of our approaches to the taxol synthesis based on this methodology was to construct the tricyclic skeleton by employing a cyclization precursor **1** (Scheme 1). Treatment of **1** with titanium tetrachloride initially produced a tricarbocycle **2**, but removal of the boronate with HF-KF in MeOH at room temperature gave an unexpected spirocyclic compound **4** along with the desired **3**.

Scheme 1



This result indicated that the tricarbocycle **3** readily undergoes Cope rearrangement to form the spiro-form **4** [4,5]. 3D structures of **3** and **4** clearly show that the 1,5-diene moiety is nicely arranged for this interconversion.



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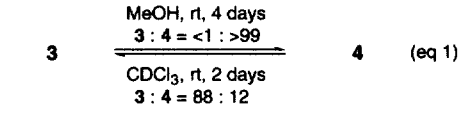
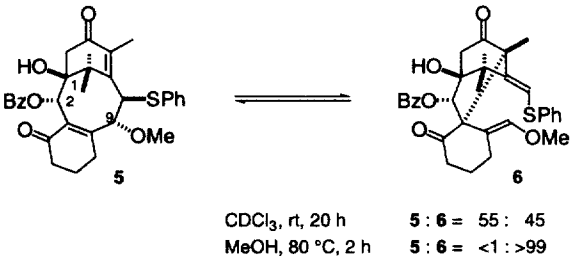
To our surprise, *the present reaction was reversible at room temperature and the product distribution was found to be highly dependent on the solvent.* Since the Cope rearrangement normally requires high reaction temperature and the solvent effect on the equilibrium composition of the products has been rarely observed [6], the above-mentioned result prompted us to investigate the Cope rearrangement of the taxane-like tricarbocycles. This paper describes details of the results and proposes the origin of the observed solvent effects.

When a mixture of **3** and **4** was kept in $CDCl_3$ at room temperature for 2 days, the taxane-like tricarbocycle **3** was predominantly obtained (**3** : **4** = 88 : 12). On the contrary, in MeOH, **3** gradually isomerized to the spirocyclic compound **4**, which was the sole product detected by ^1H NMR spectrum (**3** : **4** = <1 : >99) after 4 days (eq. 1).



(eq 1)

Similar phenomenon was also observed with the substrate **5** having the C2-benzoyloxy and C9-methoxy substituents [7]: at equilibrium in MeOH, the spirocyclic compound **6** was the sole product (since the rearrangement was quite slow, the reaction was performed at 80 °C), while the reaction in $CDCl_3$ gave an almost 1:1 mixture of **5** and **6** (eq. 2).



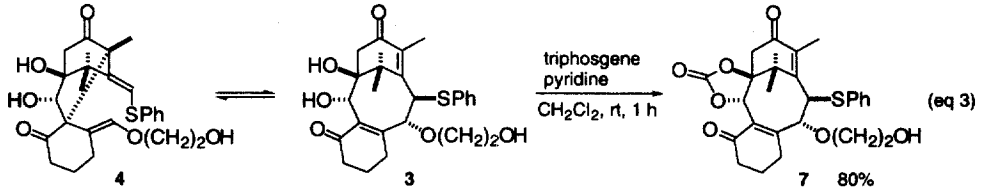
(eq 2)

These results clearly show that, in the *protic* solvent, the spirocyclic compound is formed exclusively, while the taxane-like tricarbocycle is favored in the *aprotic* solvent. In addition, the equilibrium composition of these two isomers in $CDCl_3$ is greatly affected by their C2 substituent. Judging from these experimental facts, the inter- and intramolecular hydrogen bonding around the C1 and the C2 oxygen functionalities is conceivably important for the product distribution. According to the inherent thermodynamic stability of the carbon skeletons, the spirocycle appears to be much more stable than the tricarbocycle, in which severe strain is imposed by the bridgehead double bond. The exclusive formation of the spiro-form in MeOH (the intermolecular hydrogen bonding is predominant) may support this fact. On the other hand, in the aprotic solvent ($CDCl_3$), the intramolecular hydrogen bonding may exert marked influence to reverse the thermodynamic stability of each isomer.

The molecular modeling studies suggested that tight intramolecular hydrogen bonding between the 1,2-diol moiety brings about pronounced strain in the spiro-form as compared with the taxane-like tricarbocycle. Hence, such factor would be the reason to favor the taxane-like tricarbocycle in $CDCl_3$.

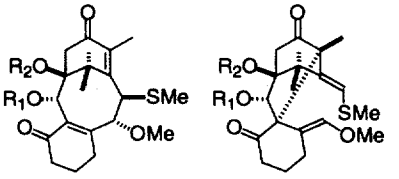
This hypothesis was also supported by the following experimental fact (eq 3). Treatment of a mixture of **3** and **4** with triphosgene gave the cyclic carbonate **7** as the sole product, which did not isomerize to the corresponding spirocyclic isomer at all. This result was

consistent with the observation that the spirocyclic isomer could not be detected in the boronate derivative **2** (Scheme 1). Presumably, the cyclic protection of the vicinal diol moiety formed a similar conformation as that of the intramolecular hydrogen bonding.



To further substantiate the origin of the observed solvent effects, the molecular orbital calculations (PM3) were performed by using the model compounds (SPh and hydroxyethyl groups were simplified to SMe and OMe groups, respectively) (Table 1) [8]. In the C1, C2-diol derivatives, comparison of each heat of formation suggested that the tricarbocycle **a** is favored over **b**, which is in good agreement with the experimental result in $CDCl_3$ (eq. 1). The greater stability of the cyclic carbonate possessing the tricarbocyclic structure (eq. 3 and table 1) also supported the above explanation. Substitution of the C2-hydroxy to the benzoyloxy group (eq. 2) would make the C2-oxygen much less basic to weaken the intramolecular hydrogen bonding effect, which results in the low selectivity observed in the reaction of **5** in $CDCl_3$. On the contrary, the heat of formation of the C1, C2-dimethoxy derivatives revealed that the spiro-isomer **b** is thermodynamically favored. Since the intramolecular hydrogen bonding does not exist in these compounds, the result of this calculation would correspond to the reactions in MeOH. Accordingly, the observed solvent effects in these reactions should be explained by the effects of the inter- and intramolecular hydrogen bonding on the relative thermodynamic stability of the two isomers.

Table 1. Comparison of thermodynamic stability



R_1	R_2	Ea	Eb	ΔE
H	H	- 178.84	- 178.31	- 0.53
- CO -		- 197.85	- 192.75	- 5.10
Me	Me	- 155.59	- 158.74	3.15

E = heat of formation (kcal/mol), ΔE = Ea - Eb

In conclusion, connection between the C1,C2-diol moiety either by intramolecular hydrogen bonding or a protecting group brought about marked stabilization to taxol-like tricarbocycles which, otherwise, would tend to undergo the Cope rearrangement to the corresponding spiro-isomers. Their product distribution was easily controlled by choosing the appropriate solvent. Since there are few examples where the solvent used has significant influence on the equilibrium composition of the Cope rearrangement, the present results may attract much attention to the aspects of the sigmatropy as well as the synthetic chemistry of the taxane diterpenoids.

Furthermore, the structure of the newly-obtained spirocyclic compounds is completely different from that of the natural taxoids, but the 3D configuration of the C2, 4, 13-oxygen functionalities is similar to those of taxol, which are known to be important for the biological activity. Thus, appropriate functionalization of the spirocycles may contribute to the development of a new lead to taxane-like biologically active compounds [9].

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References and Notes

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[4] On anionic oxy-Cope rearrangement of C9-hydroxy derivative, see Seto, M.; Sakurai, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 993-994.

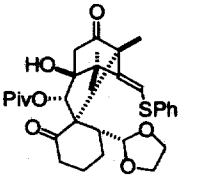
[5] Mukaiyama et. al also found a similar Cope rearrangement of the taxol AB-ring bicyclic system (the compounds **11** and **12** in their previous report; Shiina, I.; Iwadare, H.; Saitoh, M.; Ohkawa, N.; Nishimura, T.; Mukaiyama, T. *Chem. Lett.* **1995**, 781-782), but their reaction was irreversible: private communication.

[6] Hill, R. K.; "Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements" in *Comprehensive Organic Synthesis*, Trost, B. M. and Fleming, I., Ed., Vol. 5, 785-826, Pergamon Press, Oxford, 1991 and references therein.

[7] The taxane numbering system is used throughout.

[8] The calculations were performed by using SPARTAN ver 4.1.1 (PM3).

[9] Recently, several natural taxanes have been reported to exhibit multi-drug resistance (MDR) reversing activity on cancer cells (Kobayashi J.; Ogiwara A.; Hosoyama H.; Shigemori H.; Yoshida N.; Sasaki T.; Li Y.; Iwasaki S.; Naito M.; Tsuruo T., *Tetrahedron*, **1994**, *50*, 7401-7416. Kobayashi J.; Hosoyama H.; Wang X.-x.; Shigemori H.; Koiso Y.; Iwasaki S.; Sasaki T.; Naito M.; Tsuruo T. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 393-398.). This prompted us to evaluate such activity of the present spirocyclic compounds. The MDR reversing activity of the derivatives of **4** was evaluated according to the method described in our previous report (Morihira, K.; Nishimori, T.; Kusama, H.; Horiguchi, Y.; Kuwajima, I.; Tsuruo, T. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 2173-2176 and 2177-2182.) and was compared with that of verapamil, a well-known MDR reversing agent. Among the several derivatives prepared, the compound **8** was found to exhibit the same potency as verapamil. Thus, the potent activity of **8** clearly shows the possibility of the spirocyclic compounds as a new lead for MDR reversing agents.



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