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# Stereocontrolled Synthesis of Oxaspirobicycles *via* Prins-Pinacol Annulation

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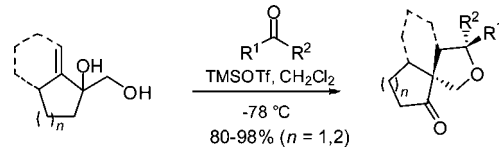
## ABSTRACT




**We have developed the stereoselective synthesis of 2-oxaspiro[*m,n*]alkane derivatives using the Prins-pinacol annulation of alkene diols with a wide range of aliphatic or aromatic aldehydes and ketones. This approach was further applied for the synthesis of oxatricyclic ring system.**

The 2-oxaspiro[4.5]decane/[4.4]nonane structural motif has been featured in a number of natural products such as bakkenolide A, wiphaphysalin F, and epansolide A (Figure 1).[1] In recent years, this type of molecular structure has been studied as an attractive synthetic target. The known synthetic methods to construct such spiro compounds involve Diels−Alder reactions of α-methylene lactone,[2] radical cyclization of bromo alkene or alkyne,[3] ring-closing metathesis reaction of diallyl oxolane derivatives,[4] lactonization of chloro sulfinyl carboxylate,[5] and metal-catalyzed insertion reaction of diazo compounds.[6] However, to date, there are only a few reports of the synthesis of substituted 2-oxaspirocyclic derivatives with quaternary carbon centers due to demanding control of stereoselectivity. In the course of our studies toward synthesis of

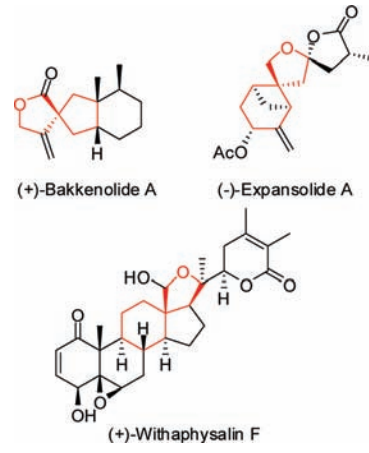



**Figure 1.** Natural products containing the 2-oxaspiro structure.

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[‡] University of Science and Technology (UST).

(1) (a) Massias, M.; Rebuffat, S.; Molho, L.; Chiaroni, A.; Riche, C.; Bodo, B. *J. Am. Chem. Soc.* **1990**, *112*, 8112. (b) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, *9*, 369. (c) Misico, R. I.; Gil, R. R.; Oberti, J. C.; Veleiro, A. S.; Burton, G *J. Nat. Prod.* **2000**, *63*, 1329.

(2) Pouwer, R. H.; Schill, H.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2007**, 4699.

(3) (a) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Tetrahedron* **2005**, *61*, 8752. (b) Nagano, H.; Ohtani, Y.; Odake, E.; Nakagawa, J.; Mori, Y.; Yajima, T. *J. Chem. Res., Synop.* **1999**, 338.

(4) Schobert, R.; Urbina-Gonzalez, J. M. *Tetrahedron Lett.* **2005**, *46*, 3657.

(5) Satoh, T.; Sugiyama, S.; Kamide, Y.; Ota, H *Tetrahedron* **2003**, *59*, 4327.

(6) Doyle, M. P.; Dyatkin, A. B. *J. Org. Chem.* **1995**, *60*, 3035.

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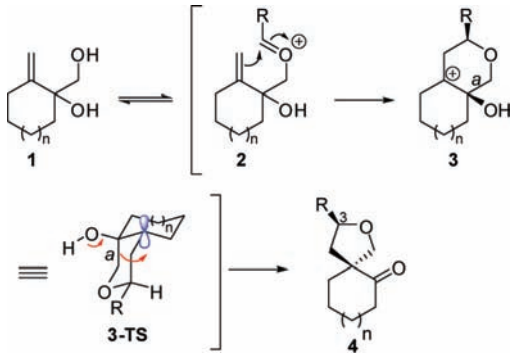
oxacyclic ring system using Prins reaction,[7] we envision that the reaction of methylene diol **1** with aldehydes in the presence of an appropriate Lewis acid would give rise to an oxaspiro bicycle **4**, as illustrated in Scheme 1. Thus, the condensation of methylene diol **1** with aldehyde under acidic conditions could generate the oxocarbenium intermediate **2**, which undergoes Prins cyclization followed by prompt pinacol rearrangement to afford 3-substituted 2-oxaspiro compound.[8] In this event, we imagine that migration of the bond *a*, which is periplanar to the empty *p* orbital, from favorable conformation **3-TS** is stereoelectronically allowed to form spiroketone **4** having a *cis* relationship between the C-3 substituent and the quaternary spirocenter.[9]

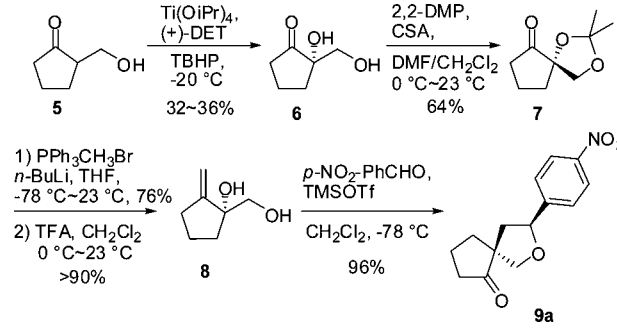
**Scheme 1.** Concept of the Prins-pinacol Annulation for the Synthesis of Oxaspirobicycles




Herein, we report an efficient, stereocontrolled synthesis of 3-substituted 2-oxaspiro[4.5]decanes/ [4.4]nonanes using Prins-pinacol annulation.

To verify our premise, we commenced with the preparation of methylene diol **8** as depicted in Scheme 2. Starting from hydroxymethyl ketone **5**,[10] we could synthesize dihydroxy ketone **6** in moderate yield using Sharpless epoxidation.[11] The diol **6** was protected as ketal **7**, which underwent Wittig olefination and subsequent deprotection to afford methylene diol **8**. With this substrate **8** in hand, we have tested Prins-

**Scheme 2.** Prins-pinacol Annulation of **8**




pinacol reactions of **8** with *p*-nitrobenzaldehyde by screening a broad range of Lewis acids including TMSOTf, $SnCl_4$, $BF_3{\cdot}OEt_2$, and $InCl_3$. Indeed, we found that the reaction of **8** with *p*-nitrobenzaldehyde in the presence of 3 equiv of TMSOTf provided the corresponding oxaspirobicycle **9a** in 96% yield as a single isomer, whereas the reactions promoted by other Lewis acids gave **9a** in lower yields. The relative stereochemistry of the compound **9a** was confirmed by analysis of the X-ray single-crystal structure (Figure 2).[12] It turned out that the relative stereochemistry between the spirocenter and the nitrophenyl group is *cis*.

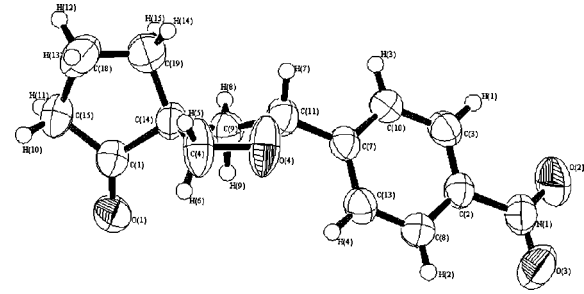


**Figure 2.** X-crystal structure of **9a** with thermal ellipsoids projected at the 50% probability level.

Encouraged by this result, we investigated the scope of this Prins-pinacol process as shown in Table 1. Initially, the spiroannulation of **8** with benzaldehyde and 4-chlorobenzaldehyde under the optimized reaction condition (3.0 equiv of TMSOTf, $CH_2Cl_2$, −78 °C, 4 h) gave the resulting oxaspiro compounds **9** stereoselectively in excellent yields (entries 1 and 2). In the case of the electron-rich 4-methoxybenzaldehyde, however, a 1:1 mixture of two diastereomers was formed exceptionally (entry 3).[13] The reactions of **1** with aliphatic aldehydes such as *n*-hexanal and isobutyraldehyde also proceeded to afford single diastereomers,

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(8) For reviews of Prins-pinacol reactions, see: (a) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. For other examples, see: (d) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. (e) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overmann, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223. (f) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romeo, A. *Org. Lett.* **2001**, *3*, 1225. (g) Ponce, A. M.; Overman, L. E. *J. Am. Chem. Soc.* **2000**, *122*, 8672. (h) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581.

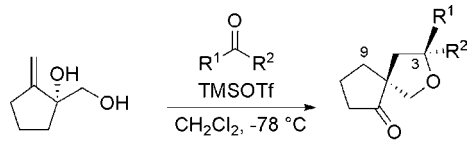
(9) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927.

(10) Taylor, R. J. K.; Wiggins, K.; Robinson, D. H. *Synthesis* **1990**, 589.

(11) Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron* **2002**, *58*, 7321. Unlike the orginal report, we found that the optical purity of **6** is only 39% ee, which was determined by $^1$H NMR analysis of *R*-(−)-α-methoxyphenyl acetate derivatives of **6**. Disappointedly, our further effort to synthesize the enantiomerically pure diol **6** has failed.

(12) See the Supporting Information for details.

**Table 1.** Scope of the Prins-pinacol Annulation of **8** with Various Aldehydes and Ketones



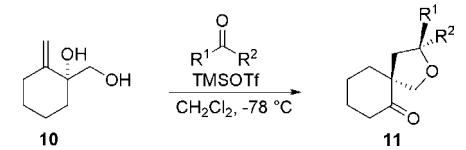

**8** **9**

| entry | $R^1$ | $R^2$ | product | yield[a] (%) |
|---|---|---|---|---|
| 1 | Ph | H | **9b** | 93 |
| 2 | 4-Cl-Ph | H | **9c** | 95 |
| 3 | 4-MeO-Ph | H | **9d** | 98[b] |
| 4 | *n*-Pent | H | **9e** | 98 |
| 5 | *i*-Pr | H | **9f** | 96 |
| 6 | $-(CH_2)_5-$ | | **9g** | 92 |
| 7 | $-(CH_2)_4-$ | | **9h** | 90 |
| 8 | *n*-Bu | Me | **9i** | 92[c] |
| 9 | Ph | Me | **9j** | 85 |

[a] Isolated yield. [b] Ratio = 1:1 (see ref 13). [c] Ratio = 2:1.

respectively (entries 4 and 5). When ketones were used as substrates, despite their low reactivities, we could effectively obtain 3,3-disubstituted 2-oxaspirobicycles in high yields (entries 6−9). While the spiroannulation of **8** with 2-hexanone gave a 2:1 mixture of two diastereomers (entry 8), the reaction of acetopheone proved to be diastereoselective, leading to only the *cis* isomer (entry 9). The structure of **9j** was determined by observing NOE enhancement between $C_3$ methyl hydrogens and $C_9$ methylene hydrogens (see the Supporting Information).

**Table 2.** Scope of the Prins-pinacol Annulation of **10** with Various Aldehydes and Ketones




**10** **11**

| entry | $R^1$ | $R^2$ | product | yield[a] (%) |
|---|---|---|---|---|
| 1 | 4-$NO_2$-Ph− | H | **11a** | 88 |
| 2 | Ph | H | **11b** | 80 |
| 3 | 4-Cl-Ph | H | **11c** | 83 |
| 4 | 4-MeO-Ph | H | **11d** | 85[b] |
| 5 | *n*-Pent | H | **11e** | 82 |
| 6 | *i*-Pr | H | **11f** | 85 |
| 7 | $-(CH_2)_5-$ | | **11g** | 62 |
| 8 | $-(CH_2)_4-$ | | **11h** | 70 |
| 9 | *n*-Bu | Me | **11i** | 65[c] |
| 10 | Ph | Me | **11j** | *d* |

[a] Isolated yield. [b] See ref 13. [c] Ratio = 2:1. [d] The corresponding ketal was formed in 60% yield.

Next, we extended our protocol to synthesize 2-oxaspiro-[4,5]decane derivatives using methylene diol **10** as a substrate (Table 2).[14] Similarly, the reaction of **10** with various aromatic and aliphatic aldehydes proceeded to generate the corresponding oxaspirobicycles exclusively although the yields of the reactions slightly decreased in comparison of the previous results. The structure of the compound **11a** was elucidated by analysis of the X-ray single crystal.[12] Ketones also worked well under our Prins-pinacol process in most cases. In the case of acetophenone, however, we could isolate only the consequent ketal derivative in 60% yield, which is presumably formed due to high stability of ketone as well as more kinetically favorable ketalization.

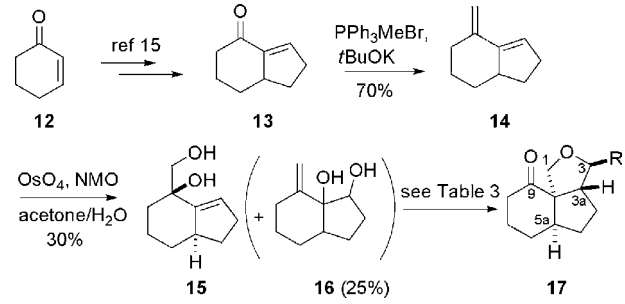
**Table 3.** Scope of the Prins-pinacol Annulation of **15** with Various Aldehydes

| entry | R | product | yield[a] (%) |
|---|---|---|---|
| 1 | Ph | **17a** | 73 |
| 2 | 4-F-Ph | **17b** | 78 |
| 3 | 3-MeO-Ph | **17c** | 75 |
| 4 | 4-Me-Ph | **17d** | 65 |
| 5 | $CH_3$ | **17e** | 81 |
| 6 | $CH_3(CH_2)_4$ | **17f** | 70 |

[a] Isolated yield.

Finally, to demonstrate the utility of our process further, we attempted the formation of the oxatricyclic ring system using diol **15** as a substrate (Table 3). Following the literature procedure,[15] we easily prepared hydrindenone **13** in two steps starting from cyclohexenone **12** (Scheme 3). Exomethylenation of **13** followed by dihydroxylation afforded the desired diol **15** in 30% yield along with a comparable amount of regioisomer **16**. The assignment of the stereochemistry of

**Scheme 3.** Formation of Oxatricyclic Ring System




**15** resulted from the assumption that the addition of $OsO_4$ to exomethylene moiety in **14** occurred in the opposite side

(13) We have realized that a 1:1 mixture of **9d** and **9d′** (diastereomer) was produced in Table 1, whereas we obtained **11d** as a single isomer in Table 2. Although we cannot clarify the discrepancy between two reactions, we assume that epimerization at the $C_3$ position took place because the carbocation intermediate generated by acid-catalyzed ring opening is significantly stabilized by the 4-methoxyphenyl group.

(14) The diol **10** was prepared following the same reaction sequences as used in Scheme 2 starting from α-hydroxymethyl cyclohexanone.

(15) (a) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045. (b) Tsantali, G. G.; Takakis, I. M. *J. Org. Chem.* **2003**, *68*, 6455.

of ring juncture hydrogen. With this substrate **15** in hand, the reaction of **15** with aromatic and aliphatic aldehydes under the previously optimized conditions gave oxatricycle compounds in high yields. Again, only the single isomers were obtained in all cases. We clearly confirmed the structure of **17** by various NMR techniques including NOE experiment (see the Supporting Information). In fact, the NOE correlation of $H_{5a}-H_1$, $H_1'-H_3$, and $Me(C_3)-H_{3a}$ in **17e** indicated that the stereochemical relationship of hydrogen($C_{5a}$)−ketone($C_9$) hydrogen($C_{3a}$)−methyl($C_3$) is *cis-trans-cis*. Accordingly, these results showed that the stereoselectivity in our Prins-pinacol process toward oxatricyclic system is well preserved. Unfortunately, attempts to carry out the reactions of **15** with ketones failed to give the desired 3,3-disubstituted products.

In summary, we have developed an efficient and stereocontrolled method for the synthesis of 2-oxaspiro[4,5]decanes/[4,4]nonanes using Prins-pinacol annulation of methylene diol promoted by Lewis acid. In this event, we have shown that a wide range of aromatic/aliphatic aldehydes and ketones are tolerated under the reaction condition. The excellent efficiency and stereoselectivity observed in this process represent an advance in the construction of molecular architectures containing substituted 2-oxaspirobicycle derivatives. In this regard, we have successfully applied this protocol to build a novel oxatricyclic ring structure. The further studies of this methodology for the total synthesis of structurally related natural products are currently in progress and will be reported in due course.

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**Supporting Information Available:** General experimental procedure, characterization data for all new compounds, and data for X-ray crystal structure analysis of **9a** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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