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Tandem Semipinacol-Type 1,2-Carbon Migration/Aldol Reaction toward the Construction of [5−6−7] All-Carbon Tricyclic Core of *Calyciphylline* A-Type Alkaloids

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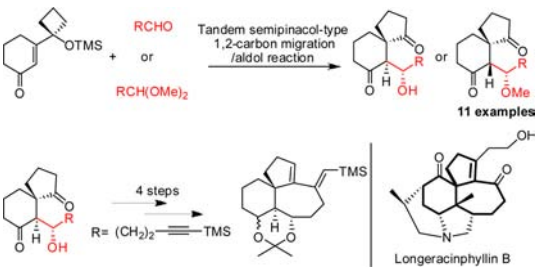
ABSTRACT



A Lewis acid promoted tandem semipinacol-type 1,2-carbon migration/aldol reaction of trimethylsilane-protected vinylogous α-ketols with aldehyde or dimethyl acetals is reported. This reaction provides a direct and rapid way for the construction of 6-substituted spiro[4.5]decanes which extensively exist in *Daphniphyllum* alkaloids. By the use of this method, further construction of a [5−6−7] all-carbon tricyclic core of *Calyciphylline* A-type alkaloids was also completed.

Calyciphylline A-type alkaloids, as important members of *Daphniphyllum* alkaloids, are synthetically challenging molecules.[1,2] Because of their novel structural skeletons, they have attracted numerous attention from organic chemists.[3] However, there has been no report about their total synthesis until now. 6-Substituted spiro[4.5]decanes which contain a spirocyclic all-carbon quaternary center, as the key structural motifs, commonly exist in *Calyciphylline* A-type alkaloids (Figure 1). How to directly and rapidly construct this unit is the key and challenging step for the syntheses of these molecules.

Recently, we have reported a chiral amine and Brønsted acid catalyzed asymmetric semipinacol-type 1,2-carbon migration[4] of vinylogous α-ketols to synthesize chiral spiro-[4.5]decane-1,7-diketones.[5] This protocol offers a feasible strategy for the construction of 6-substituted spiro[4.5]-decanes via a tandem manner (Scheme 1). However, efforts to utilize the enamine intermediate for the expected tandem

(1) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936.

(2) For isolation of *Calyciphylline* A-type alkaloids, see: (a) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895. (b) Takatsu, H.; Morita, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279. (c) Chen, X.; Zhan, Z.-J.; Yue, J.-M. *Helv. Chim. Acta* **2005**, *88*, 854. (d) Yang, S.-P.; Zhang, H.; Zhang, C.-R.; Cheng, H.-D.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 79. (e) Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 553. (f) Di, Y.-T.; He, H.-P.; Lu, Y.; Yi, P.; Li, L.; Wu, L.; Hao, X.-J. *J. Nat. Prod.* **2006**, *69*, 1074. (g) Li, Z.-Y.; Chen, P.; Xu, H.-G.; Yang, Y.-M.; Peng, S.-Y.; Zhao, Z.-Z.; Guo, Y.-W. *Org. Lett.* **2007**, *9*, 477. (h) Mu, S.-Z.; Li, C.-S.; He, H.-P.; Di, Y.-T.; Wang, Y.; Wang, Y.-H.; Zhang, Z.; Lü, Y.; Zhang, L.; Hao, X.-J. *J. Nat. Prod.* **2007**, *70*, 1628. (i) Li, C.-S.; Di, Y.-T.; Zhang, Q.; Zhang, Y.; Tan, C.-J.; Hao, X.-J. *Helv. Chim. Acta* **2009**, *92*, 653.

(3) For recent synthetic approaches to *Calyciphylline* A-type alkaloids, see: (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461. (b) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812. (c) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132. (d) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684. (e) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. *J. Org. Chem.* **2012**, *77*, 6307.

(4) For recent reviews on semipinacol rearrangement, see: (a) Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823. (b) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523. (c) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207.

(5) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626.

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aldol reaction failed.[6] The reason might be the instability of the enamine intermediate which can be quickly isomerized to imine and quenched by water formed at the beginning to give the diketone product. On the basis of these results, we proposed that the use of proper Lewis acid would probably initiate the semipinacol-type 1,2-carbon migration of trimethylsilane-protected vinylogous α-ketols to give enolate intermediates which could further undergo a Lewis acid promoted aldol reaction[7] to construct 6-substituted spiro[4.5]decane-1,7-diones (Scheme 1). Herein, we present our preliminary results on this protocol and its application in the synthesis of [5−6−7] all-carbon tricyclic core of *Calyciphylline* A-type alkaloids.

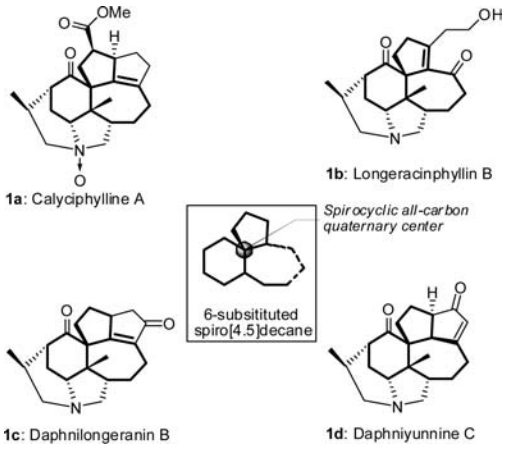
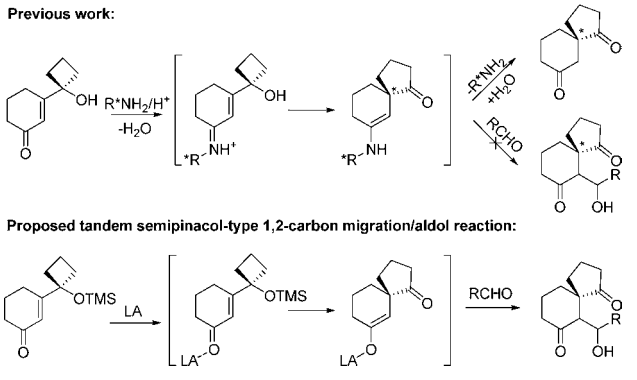


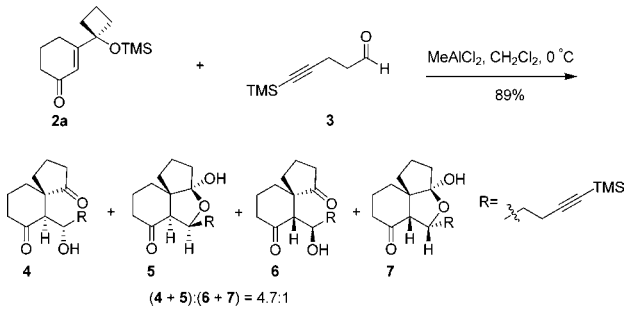
Figure 1. Selected *Calyciphylline* A-type alkaloids.

Scheme 1. Previous Work and Proposed Tandem Semipinacol-Type 1,2-Carbon Migration/Aldol Reaction



We first studied our proposed tandem semipinacol-type 1,2-carbon migration/aldol reaction of trimethylsilane-protected vinylogous α-ketol **2a** with aldehyde **3**. As shown in Scheme 2, treatment of **2a** with 1.2 equiv of aldehyde **3** and 1.2 equiv of $MeAlCl_2$ in CH_2Cl_2 at 0 °C, the tandem reaction could be finished within 20 min and provided 6-substituted spiro[4.5]decane-1,7-diones **4** and **6**, hemiketals **5** and **7** in 89% overall yield [(**4**+**5**):(**6**+**7**) = 4.7:1]. It should be noted that other Lewis acids, such as $TiCl_4$, Et_3Al, Et_2AlCl, and TMSOTf, were not effective for this reaction. The hemiketals **5** and **7** should be derived from corresponding diketones **4** and **6** under the Lewis acid conditions. This was confirmed by the increased ratio of **5** and **7** upon prolonging the reaction time. Among the products, the diketone **4** and hemiketal **5** could not be thoroughly separated through column chromatography, and the ratio of them was about 10:1 which was indicated by ^1H NMR. However, the diketone **6** and hemiketal **7** were inseparable. Furthermore, the relative configuration of hydroxyl diketone **4** was verified at a late stage by X-ray structure of **16**, of which the 6-H is *cis* to the 1-carbonyl group and *syn* to the hydroxyl group.

Scheme 2. Study on Tandem Semipinacol-Type 1,2-Carbon Migration/Aldol Reaction of Trimethylsilane-Protected Vinylogous α-Ketol and Aldehyde



To prevent the formation of the hemiketals, the aldehyde was replaced by dimethyl acetals.[8] To our delight, the tandem reaction could also take place under the standard procedure, and the results are summarized in Table 1. Very interestingly, unlike that for compound **4**, the 6-H of the major product **9** is *trans* to the 1-carbonyl group and *anti* to the methoxyl group, which was confirmed by the X-ray crystallography analysis of compound **9h** (Figure 2).[9] This result indicated that the aldol reaction might go through a nonchelated transition state with the introduction of acetal moiety. As shown in Table 1, trimethylsilane-protected vinylogous α-ketol **2a** could react with various dimethyl acetals giving the corresponding 6-substituted spiro[4.5]-decane-1,7-diones. Moderate to good yields and diastereoselectivities could be obtained. Normally, acetal substrates with longer chains could give better diastereoselectivities

(6) Recently, we also reported a one-pot reaction to construct chiral 6-hydroxy spiro[4.5]decane-1,7-diones: Li, B.-S.; Zhang, E.; Zhang, Q.-W.; Zhang, F.-M.; Tu, Y.-Q.; Cao, X.-P. *Chem. Asian J.* **2011**, *6*, 2269.

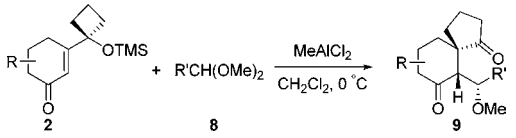
(7) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

(8) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

(9) CCDC-897943 for **9h** and CCDC-852779 for **16** contain the the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

than the shorter ones. Acetals derived from propargyl or aromatic aldehydes afforded better yields than those from aliphatic aldehydes (Table 1, entries 4, 8, and 9 compared with entries 1−3 and 5−7). The results might be due to the elimination of methanol by dimethyl acetals of aliphatic aldehydes which could quench the enolate intermediate.[10] In addition, acetals bearing a silyl ether could also participate well in this tandem reaction with good yields (Table 1, entries 9 and 11). Also, geminal dimethyl substituents at the C-5 position on the cyclohexanone of trimethylsilane-protected vinylogous α-ketol showed no retardation of this tandem reaction (Table 1, entries 10 and 11). However, efforts to construct two continuous all-carbon quaternary centers by this tandem reaction failed (Table 1, entry 12). Although we mainly focused on the syntheses of 6-substituted spiro[4.5]decanes, we had also tried to synthesize other ring systems. Unfortunately, when we changed the cyclobutanol to cyclopentanol or cyclohexanol, the semipinacol-type 1,2-carbon migration could not occur. When the substrate with the cycloheptyl instead of the cyclohexyl core ring was subjected to the reaction, the major product was the spiro[4.6]undecane-1,7-dione. At last, it should be noted that for all products in Table 1, the major isomers of **9a**, **9e**, and **9g**−**k** could be easily separated by silica gel column chromatography from the remaining isomers; the diastereomers of **9b**−**c** and **9f** could be partially separated; however, the diastereomers of **9d** were inseparable.

Table 1. Tandem Semipinacol-Type 1,2-Carbon Migration/Aldol Reaction of Trimethylsilane-Protected Vinylogous α-Ketol and Dimethyl Acetals[a]



entry	substrate	acetal	yield[%][b] (product)	dr[c]
1	**2a**	$CH_3CH(OMe)_2$(**8a**)	66(**9a**)	4.4:1:0.26
2	**2a**	$CH_3(CH_2)_5CH(OMe)_2$(**8b**)	76(**9b**)	6.4:1:0.35
3	**2a**	$CH_3(CH_2)_7CH(OMe)_2$(**8c**)	74(**9c**)	6.6:1:0.27
4	**2a**	$PhCH(OMe)_2$(**8d**)	95(**9d**)	1.7:1:0.08
5	**2a**	$PhCH_2CH(OMe)_2$(**8e**)	69(**9e**)	9:1:0.16
6	**2a**	$PhCH_2CH_2CH(OMe)_2$(**8f**)	68(**9f**)	10:1:0.6
7	**2a**	$TMSC{\equiv}C(CH_2)_2CH(OMe)_2$(**8g**)	49(**9g**)	7.8:1:0.6
8	**2a**	$PhC{\equiv}CCH(OMe)_2$(**8h**)	96(**9h**)	5.9:1:0.17
9	**2a**	$TBSOCH_2C{\equiv}CCH(OMe)_2$(**8i**)	78(**9i**)	7.1:1:0.28
10		$PhCH_2CH(OMe)_2$(**8e**)	70(**9j**)	8:1
11		$TBSOCH_2C{\equiv}CCH(OMe)_2$(**8i**)	86(**9k**)	7.7:1:0.3
12		$PhCH_2CH(OMe)_2$(**8e**)	—	—

[a] For experimental details, see the Supporting Information. [b] Combined yield of isolated product after column chromatography. [c] The dr value was determined by ^{1}H NMR.

(10) For the elimination of methanol by dimethyl acetals, see: Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449.

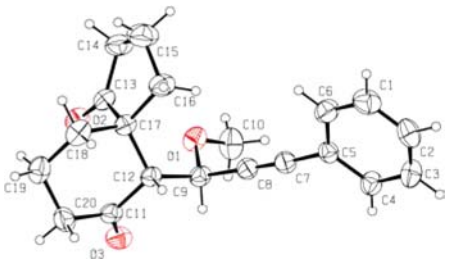
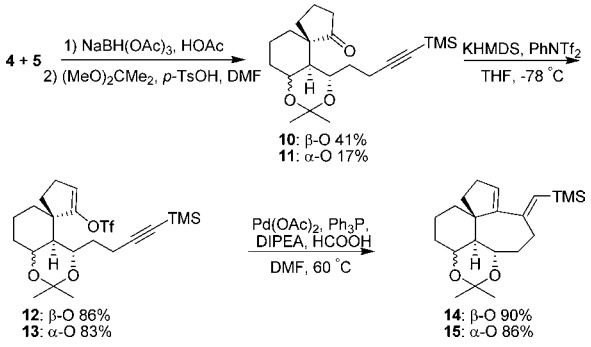


Figure 2. X-ray structure of **9h**.

After successful development of the tandem semipinacol-type 1,2-carbon migration/aldol reaction, we applied it to the synthesis the [5−6−7] all-carbon tricyclic core of *Calycphyilline* A-type alkaloids from the corresponding 6-substituted spiro[4.5]decane-1,7-diones. Compound **4** (mixed with **5**) of the first studied tandem reaction was chosen as the starting material (Scheme 3). Selective reduction of the cyclohexanone moiety of the mixture with $NaBH(OAc)_3$ in acetic acid at room temperature[11] followed by protection of the 1,3-diol using 2,2-dimethoxypropane provided ketones **10** in 41% yield and **11** in 17% yield over two steps. Ketones **10** and **11** were then converted into enol triflates **12** and **13** by quenching the corresponding potassium enolates with $PhNTf_2$ in 86% and 83% yield, respectively. Treatment of **12** or **13** with $Pd(OAc)_2$ under the reductive condition afforded [5−6−7] tricyclic product **14** in 90% yield or **15** in 86% yield successfully.[12] The relative stereochemistry of **14** was confirmed by X-ray diffraction of crystalline diol **16** obtained by desilylation and deprotection of **14** (Scheme 4).[9]

Scheme 3. Synthesis of the [5−6−7] All-Carbon Tricyclic Core of *Calyciphylline* A-Type Alkaloids

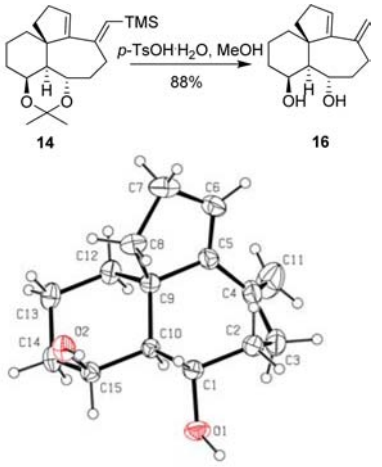


In conclusion, we have developed a tandem semipinacol-type 1,2-carbon migration/aldol reaction of trimethylsilane-protected vinylogous α-ketols with aldehyde or dimethyl

(11) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.

(12) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325.

Scheme 4. Relative Stereochemistry of **16**



acetals. 6-Substituted spiro[4.5]decane-1,7-diones could be easily and rapidly synthesized by this protocol. Subsequently, the [5−6−7] all-carbon tricyclic core of *Calyciphylline* A-type alkaloids has been rapidly constructed for the first time. It demonstrates that the newly developed tandem reaction is a potentially useful method in the total synthesis of polycyclic nature products which contain the structural motif of 6-substituted spiro[4.5]decane. Further studies toward a total synthesis of *Calyciphylline* A-type alkaloids using this protocol are underway in our laboratory.

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Supporting Information Available. NMR spectra of products and X-ray crystallographic data for **9h** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.