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# A Novel and Stereoselective Spiroannelation: A Facile Access to Aphidicolane and Stemodane B/C/D-Ring Systems

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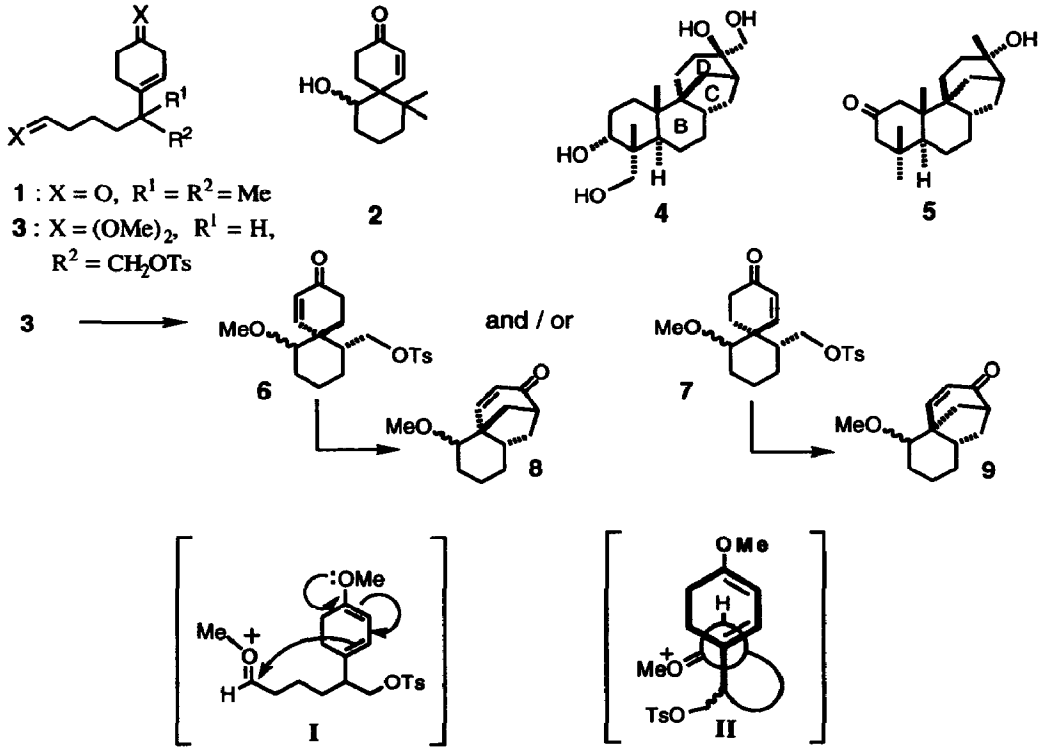
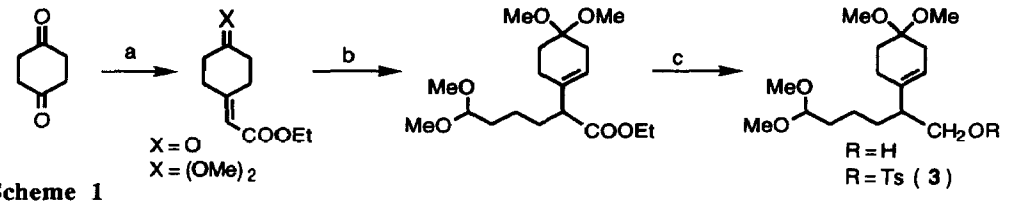
***Abstract:*** *Spiro[5.5]undecane derivatives 6A and 7S were obtained in moderate stereoselectivity by the intramolecular spiroannelation reaction of a bis-acetal 3 promoted by TMSOTf, and the selectivity was reversed by changing the solvent from acetonitrile to THF.*

The development of the method for constructing spirocyclic ring systems continues to attract interest in synthetic organic chemistry.[1] As the spirocenter carbon atoms found in various natural products are asymmetric, the stereoselective construction of them is an important subject. Although several methodologies on the synthesis of spiro[5.5]undecane skeleton have been reported so far,[1] there are a few reports controlling the stereoselectivity at the spiro center.[2] Yamada and Niwa *et al* reported an acid-catalyzed spiroannelation reaction for a 4-substituted 3-cyclohexen-1-one derivative (**1**) to afford a spiro-enone (**2**), but nothing was referred to the stereoselectivity.[3] Being stimulated by this work, we set to the task of developing a new stereoselective spiroannelation reaction by the aid of Lewis acids. Our substrate for the spiroannelation is a bis-acetal (**3**), which installs suitable functionalities for the syntheses of the B/C/D-ring systems of aphidicolane (**4**) and stemodane diterpenes (**5**).[4] Our initial goal is the stereoselective construction of the B/C/D-ring systems of both



diterpenes from the common intermediate (**3**). In this letter, we describe that the reverse stereoselectivity was observed in the spiroannelation reaction of **3** mediated by trimethylsilyl triflate (TMSOTf) in acetonitrile and in tetrahydrofuran (THF).

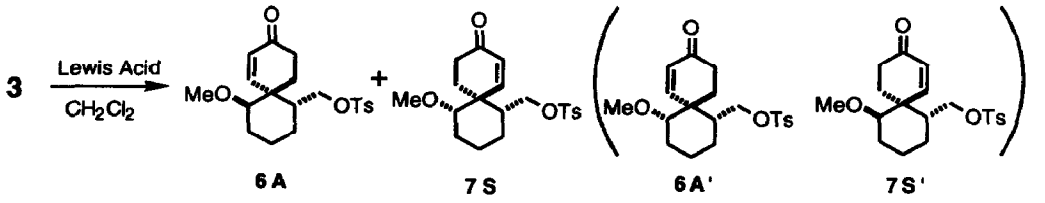
The products from the bis-acetal **3** are classified into two types of spirocyclic compounds (**6** and **7**). In the compound **6**, the relationship of the carbon-carbon double bond and the tosyloxymethyl group is *cis*, and in **7** it is *trans*. The former is aphidicolane-type (A-type) and the latter is stemodane-type (S-type), because treatment of **6** and **7** with a base would produce an A-type tricyclic enone **8** and an S-type compound **9**, respectively.[5] When the plausible intermediate (**I**) takes an anti-periplanar conformation (**II**) regarding the enol ether and the oxonium ion moiety to minimize the electrostatic repulsion of the positively charged oxygen as suggested by Murata and Noyori,[6] a considerable extent of stereoselectivity is expected. So, predominant formation of either **6** or **7** is expected under appropriate conditions using various Lewis acids and solvents. After the synthesis of **3** starting from 1,4-cyclohexanedione (Scheme 1), we investigated first the spiroannelation reaction of **3** with various Lewis acids in $CH_2Cl_2$ (Table 1).




**Scheme 1**

a: 1) $(EtO)_2P(O)CH_2COOEt$, NaH, THF (91 %) 2) $CH(OMe)_3$, p-TsOH, MeOH (96 %); b : LDA, HMPA, $(MeO)_2CH(CH_2)_3Br$ (78 %); c: 1) LAH, $Et_2O$ (94 %); 2) TsCl, DMAP, $CH_2Cl_2$ (97 %)

**Table 1**



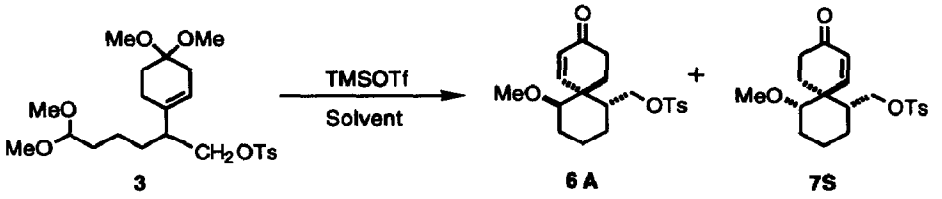

| Lewis Acid | Temp.(°C) | Time (min) | 6A : 7S* | Yield (%) |
|---|---|---|---|---|
| TMSOTf | −78 | 40 | 57 : 43 | 82 |
| TBDMSOTf | 0 | 60 | 50 : 50 | 74 |
| $TiCl_4$ | −78 | 150 | — | trace |
| $Ti(Oi\text{-}Pr)_2Cl_2$ | −78 | 60 | 60 : 40 | 31 |
| $Ti(Oi\text{-}Pr)_4$ | −78 → rt | 900 | no reaction | |
| $AlCl_3$ | −78 → rt | 120 | — | trace |
| $BF_3{\cdot}Et_2O$ | −78 | 40 | — | trace |
| $SnCl_4$ | −78 | 40 | — | 0 |

* Diastereomeric ratio was determined by 200 MHz $^1$H-NMR.

The results show that treatment with TMSOTf afforded the highest yield in this reaction. As expected, two (out of four) products (**6A** and **7S**) were obtained. Namely, the relationship of the methoxyl group and the carbon-carbon double bond was regulated to *trans* in both compounds. Neither *cis* compound **6A'** nor **7S'** was

isolated.[7] However, no stereoselectivity between **6A** and **7S** was demonstrated with the listed Lewis acids in $CH_2Cl_2$.

**Table 2**

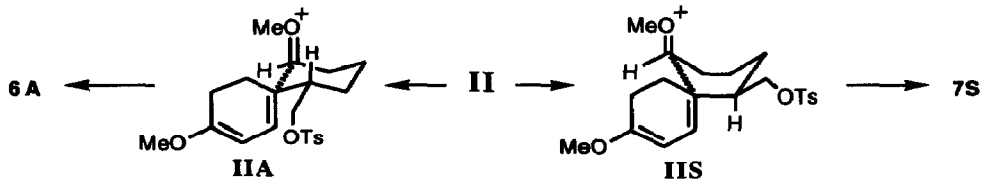



**3** **6A** **7S**

| Solvent | Temp.(°C) | Time (min) | 6A : 7S* | Yield (%) |
|---|---|---|---|---|
| $CH_3CN$ | –48 | 30 | 71 : 29 | 77 |
| *n*-PrCN | –78 | 40 | 67 : 33 | 73 |
| $CHCl_3$ | –63 | 30 | 60 : 40 | 40 |
| $CH_2Cl_2$ | –78 | 40 | 57 : 43 | 82 |
| Toluene | –78 | 40 | 43 : 57 | 72 |
| DME | –58 | 60 | 50 : 50 | 40 |
| Dioxane | 20 | 40 | 48 : 52 | 36 |
| THF | –78 | 80 | 26 : 74 | 52 |
| $Et_2O$ | –78 | 60 | — | 0 |
| $CH_3NO_2$ | –29 | 30 | — | 0 |

* Diastereomeric ratio was determined by 200MHz $^1$H-NMR.

Next, we tried the reactions using TMSOTf in various solvents (Table 2). It was found that changing the solvent from $CH_2Cl_2$ to $CH_3CN$ or THF increased the stereoselectivity, and moreover interestingly the opposite selectivity was found in those solvents. Although we do not have reasonable account for the solvent effects at the present time, a plausible reaction pathway for the exclusive formation of **6A** and **7S** was considered as follows. At first, TMSOTf converted the ketal moiety of **3** to a dienol ether and the acetal to an oxonium ion to form an intermediate (**I**). Next, at the transition state (**II**), two conformations (**IIA** and **IIS**), in which the tosyloxymethyl groups are located in an equatorial position, are possible. The former **IIA** is a chair-like transition state and subsequently forms an axial methoxyl group. On the other hand, the latter **IIS** is a boat-like one and affords an equatorial methoxyl group. Probably, there is little energy difference in the transition states **IIA** and **IIS** in $CH_2Cl_2$. Then **6A** and **7S** were obtained in a similar ratio. It is obscure that how the transition states were affected by the solvents.




The finding of a opposite selectivity by means of changing the solvents is very useful for the stereoselective syntheses of aphidicolane and stemodane diterpenes. Further investigation for the higher stereoselectivity and an optically active version are now in progress in our laboratory.

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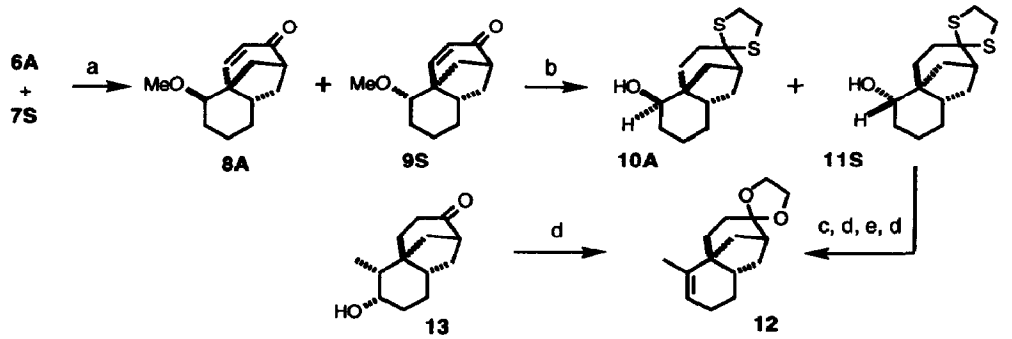
7) Stereochemistry of **6A** and **7S** was determined as follows. An inseparable mixture of **6A** and **7S** was treated with KO*t*-Bu to afford a mixture of **8A** and **9S**, which was separated by chromatography. After hydrogenation, each of them was treated with ethanedithiol in the presence of $BF_3$•$Et_2O$ to afford hydroxy-thioketals **10A** and **11S**, respectively. Compound **11S** was converted to the ketal-olefin **12** by deprotection of the thioketal, ketalization with ethylene glycol, PCC oxidation, addition of MeLi, and then treatment with *p*-TsOH in the presence of ethylene glycol in refluxing benzene. Compound **12** was identical with the compound prepared from the keto-alcohol **13** synthesized independently by us[5] *via* ketalization accompanied with simultaneous dehydration. The configuration of the methoxyl group of **6A** and **7S** was revealed by the coupling constant of the carbinol protons of **10A** (t-like, $J$ = 2 Hz) and **11S** (dd, $J$ = 11, 5 Hz).


a : t-BuOK, $Et_2O$; b : 1) separation 2) $H_2$, Pd-C 3) ethanedithiol, $BF_3$•$Et_2O$; c : $HgClO_4$, MeOH, $CHCl_3$; d : p-TsOH, ethylene glycol, $C_6H_6$, reflux; e : 1) PCC, $CH_2Cl_2$ 2) MeLi, $Et_2O$

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