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# Dramatic Solvent Effect on the Diastereoselectivity of Michael Addition: Study toward the Synthesis of the ABC Ring System of Hexacyclinic Acid

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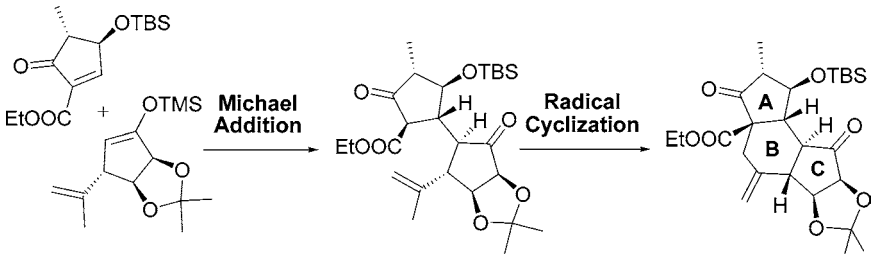
## ABSTRACT




**During our studies toward the synthesis of the ABC ring system of hexacyclinic acid, we have observed a dramatic influence of the solvent on both our key steps. The diastereoselectivity of the intermolecular Michael addition could be totally reversed by changing the polarity of the solvent, and trifluoroethanol was found to be the optimal solvent for the following Mn(III)-promoted radical cyclization.**

Hexacyclinic acid (**1**) was isolated from *Streptomyces cellulosae* subspecies *griseorubiginosus* (strain S1013) and was shown to exhibit some cytotoxic activity (Figure 1).[1]

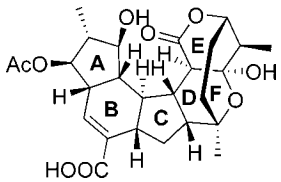



**Figure 1.** Hexacyclinic acid **1**.

The complex and challenging structure of this molecule has drawn interest among several groups, leading to diverse strategies for the construction of its ring system. Clarke has reported the synthesis of the AB and DEF ring systems,[2] while Landais[3] and Kalesse[4] have published routes to ABC tricycles. However, the total synthesis of hexacyclinic acid has not been reported yet.

Our strategy for the synthesis of the ABC ring system of hexacyclinic acid involves a convergent route (Scheme 1). Target molecule **2** would arise from $\beta$-keto ester **3** via a decarboxylation and functional group interconversions (FGI). We envisioned that compound **3** could be obtained by a radical-derived addition of the $\beta$-keto ester onto the isopropenyl moiety of **4**. This $\beta$-keto ester **4** would in turn result

(1) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *18*, 3258−3261.

(2) (a) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221−4224. (b) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560−1561. (c) Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron Lett.* **2004**, 927−929. (d) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, 353−363.

(3) James, P.; Felpin, F.-X.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 7985−7995.

(4) (a) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889−3892. (b) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485−3488.

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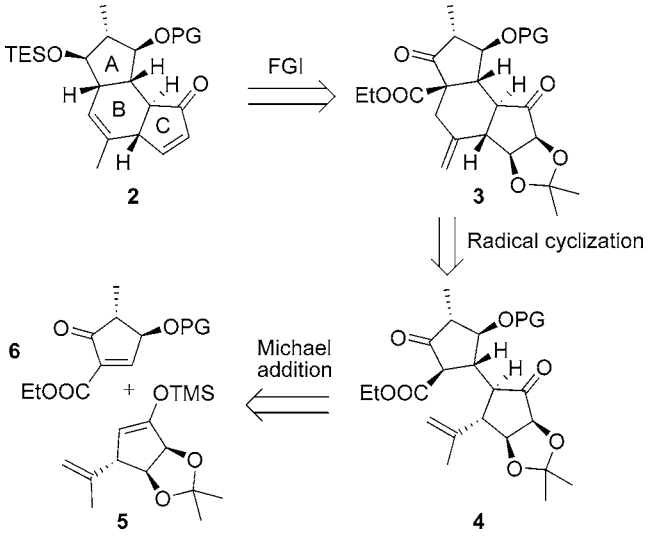
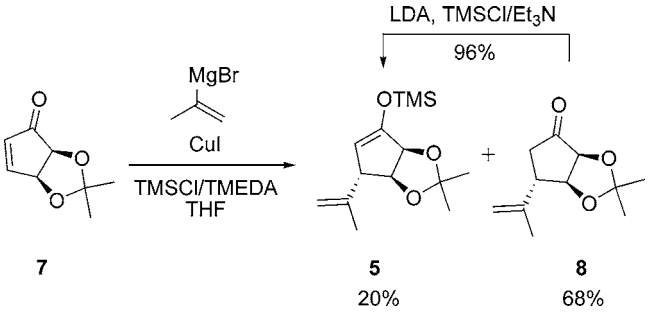
**Scheme 1.** Retrosynthetic Analysis of the ABC Tricycle of **1**




from a challenging diastereoselective Michael addition of enol ether **5** to enone **6**.[5]

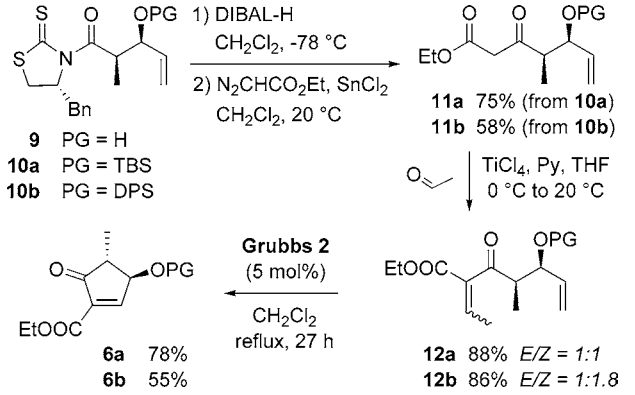
Conjugate addition of isopropenylmagnesium bromide to the known enantiopure enone **7**[6] afforded the desired enol ether **5** together with the corresponding ketone **8**, which was then easily converted into enol ether **5** in high yield (Scheme 2). Attack of the organometallic reagent occurs exclusively on the convex face of the enone.[7]

**Scheme 2.** Synthesis of Enol Ether **5**




We next focused on the synthesis of two Michael acceptors, differing by the silyl protecting group on the hydroxy substituent. The synthesis of enones **6a** and **6b** is based on a ring-closing metathesis developed in our group, involving a doubly deactivated trisubstituted olefin.[8] The diene precursors were easily prepared in four steps from known aldol **9**[9] via silyl ethers **10a** and **10b** (Scheme 3). The ring-closing

**Scheme 3.** Synthesis of Michael Acceptors **6a** and **6b**




metathesis proceeded smoothly for both dienes and furnished cyclopentenones **6a** and **6b** in 78 and 55% yield, respectively.

With all partners in hand, we embarked on a study of the Michael addition. We supposed that the stereoselectivity of this reaction under kinetic conditions would be entirely controlled by steric factors.[10] However, treatment of enol ether **5** with butyllithium for in situ generation of the enolate and subsequent addition of this enolate to enone **6a** in the presence of a Lewis acid ($ZnCl_2$) in a mixture of THF and toluene (4:1) afforded the Michael adducts **4a** (desired isomer) and **4′a** in a 2.5:1 ratio. The stereochemistry of both diastereomers was proven by NOESY experiments (Figure 2), apart from the configuration of the ethoxycarbonyl substituent, which was assumed from literature precedents.[10]

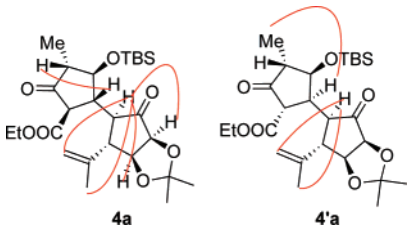



**Figure 2.** NOE observed for **4a** and **4′a**.

The lack of total stereocontrol was unexpected. The formation of isomer **4′a** results from an attack of the enolate on the same side as the sterically hindered OTBS substituent of the enone. Even more surprisingly, use of the more hindered Michael acceptor **6b** did not improve the selectivity in favor of the desired adduct, and a diastereomeric ratio of 1:1 was obtained.

In light of the work of Ikeda,[10] we rationalized that there might be a complexation of the lithium ion of the enolate

(5) The presence of the exocyclic ester moiety is required for an efficient Michael addition; see: Funel, J.-A. Ph.D. Thesis, Ecole Polytechnique, 2004. For related publications from our laboratory, see: (a) Funel, J.-A.; Prunet, J. *J. Org, Chem.* **2004**, *69*, 4555−4558. (b) Funel, J.-A.; Prunet, J. *Chem. Commun.* **2005**, 4833−4835.

(6) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. *Org. Lett.* **2005**, *7*, 5075−5078 and references cited therein.

(7) Johnson, C. R.; Chen, Y.-F. *J. Org. Chem.* **1991**, *56*, 3344−3351.

(8) Toueg, J.; Prunet, J. *Synlett* **2006**, 2807−2811.

(9) (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

(10) Yakura, T.; Tanaka, K.; Kitano, T.; Uenishi, J.; Ikeda, M. *Tetrahedron* **2000**, *56*, 7715−7721.

by the OTBS group of the Michael acceptor to explain the formation of **4′a** (Figure 3).

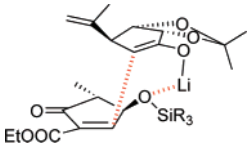
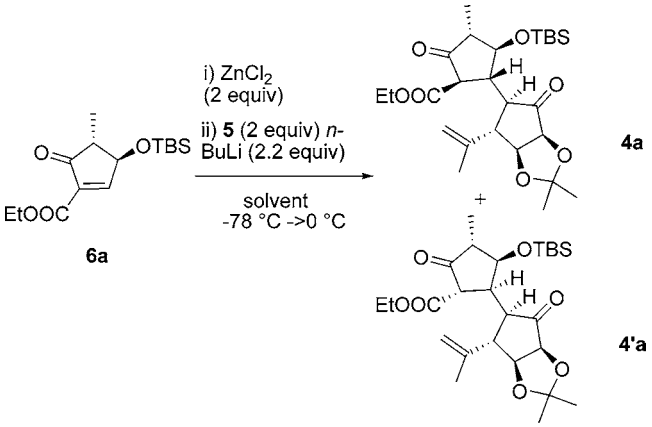



**Figure 3.** Proposed approach for the formation of **4′a**.

To address this problem, we reasoned that increasing the polarity of the solvent should favor the "uncomplexed" approach of the nucleophile on the less hindered face of the Michael acceptor. Indeed, it appears that the proportion of the desired isomer **4a** increases with the polarity of the solvent (Table 1). The best selectivity was obtained using a

**Table 1.** Michael Addition



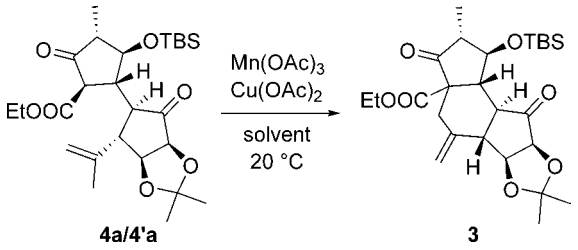

| | solvent | yield (%) | **4/4′** |
|---|---|---|---|
| 1 | $Et_2O$ | 60 | 1:7 |
| 2 | 1:4 THF/toluene | 50 | 1:2.5 |
| 3 | 4:1 THF/toluene | 46 | 2.5:1 |
| 4 | 4:1 DMF/THF | 43 | 7:1 |
| 5 | 4:1 DMF/THF | 60 | 7:1[a] |

[a] Reaction run with 3 equiv of enol ether **5** and 3.3 equiv of *n*-BuLi.

mixture of DMF and THF (4:1), leading to a mixture of **4a** and **4′a** in a 7:1 ratio. Noteworthy is the importance of a careful monitoring of the temperature to obtain reproducible diastereomeric ratios. Besides, the yield could be increased to 60% using 3 equiv of enolate instead of 2 equiv.[11]

With an optimized Michael addition step in our hands, we then turned our attention to the radical cyclization, using $Mn(OAc)_3$ to generate the radical from the $\beta$-keto ester. This step was carried out on the unseparated mixture of **4a** and **4′a**. Once again, the choice of solvent proved crucial (Table

**Table 2.** Radical Cyclization




| | solvent | time (h) | yield[a] (%) |
|---|---|---|---|
| 1 | MeCN | 3 | |
| 2 | EtOH | 3.5 | |
| 3 | MeOH | 3.5 | 10 |
| 4 | AcOH | 1.5 | 20−41 |
| 5 | 10:1 $CF_3CH_2OH$/AcOH | 1.5 | 50 |

[a] Yields are calculated from **4a** only.

2), as the yield increased with the solvent acidity.[12,13] However, the results obtained in acetic acid were not reproducible, which is probably due to the presence of acid-sensitive functionalities such as the acetonide. A switch to 2,2,2-trifluoroethanol, displaying an intermediate p$K_a$ value between those of methanol and acetic acid, allowed us to isolate the tricyclic compound **3** in a reasonable and reproducible 50% yield. Yet, it is necessary to use acetic acid as cosolvent in order to dissolve the copper acetate.

Noteworthy is the fact that isomer **4′a** seems to lead only to degradation products, whereas **4a** undergoes cyclization, affording **3** as a single diastereomer. The configuration of the carbon bearing the ethoxycarbonyl group could not be determined by NOE experiments. We anticipated that a *cis,trans* ring junction was more likely than a *trans,trans* ring junction for this 5,6,5 ring system.

In order to resolve this stereochemical ambiguity, we pursued the synthesis by a Luche reduction. We hoped that cerium(III) chloride would be complexed by the oxygens of the diketone **3**, thus shielding its $\beta$-face and leading to a diastereoselective reduction from the α-face. This would allow us to generate the last stereocenter of the A-ring of hexacyclinic acid with the desired stereochemistry. The reaction afforded a mixture of hemiketal **13** and alcohol **14** (Scheme 4).[14] It seems that cerium(III) chloride induces the formation of hemiketal **13**, which is then reduced to **14**. The hemiketal acts as a protecting group for the ketone located on the C-ring, rendering the reaction not only diastereoselective[15] but also regioselective.

We assumed that hemiketals **13** and **14** were stabilized by the presence of a hydrogen bond between the hydroxyl

(11) An inseparable mixture of ketone **8** and Michael acceptor **6a** was obtained along with adducts **4a** and **4′a**, which prevented us from calculating a yield based on recovered starting material.

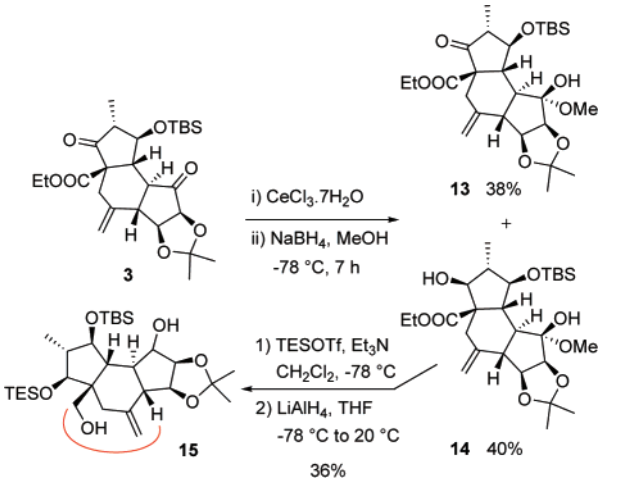
(12) (a) Snider, B. M. *Chem. Rev.* **1996**, *96*, 339−363. (b) Melikyan, G. G. *Org. React.* **1997**, *49*, 427−675. For a recent example of Mn(III)-promoted radical cyclization, see: (c) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345−4348.

(13) When the reaction was carried out in nucleophilic solvents such as MeOH or EtOH, hemiketals of type **13** were formed, which partly explains the observed low yields.

(14) Full conversion to alcohol **14** has not been optimized.

(15) The stereochemistry of **14** was proven by NOESY experiments.

**Scheme 4.** Luche Reduction




of the hemiketal and one of the oxygens of the $\beta$-face (the carbonyl of the ester or an oxygen of the acetonide). This hypothesis was confirmed by molecular modeling.[16]

Since the configuration of the center bearing the ethoxycarbonyl substituent could still not be determined by NOESY experiments, the ester moiety was reduced to the corresponding primary alcohol **15** after protection of the A-ring alcohol as the TES ether. The $\beta$-configuration of the primary alcohol substituent was determined unambiguously by NOESY experiment, as shown in Scheme 4.

In conclusion, we have synthesized a precursor of the ABC ring system of hexacyclinic acid using a diastereoselective Michael addition and a radical cyclization as key steps. The choice of the solvent proved decisive in both reactions. In the case of the Michael addition, a polar solvent was necessary to favor the formation of the desired Michael adduct. For the radical cyclization, 2,2,2-trifluoroethanol enabled us to obtain good and reproducible yields. Finally, a Luche reduction allowed us to install successfully the last stereocenter of the A-ring. Further work toward the synthesis of hexacyclinic acid is currently in progress in our laboratory.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Calculation was run with *ChemDraw 11.0* (CambrideSoft) using an MM2 force field.