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Tandem Intramolecular Michael-Aldol Reaction as a Tool for the Construction of the C-Ring of Hexacyclinic Acid

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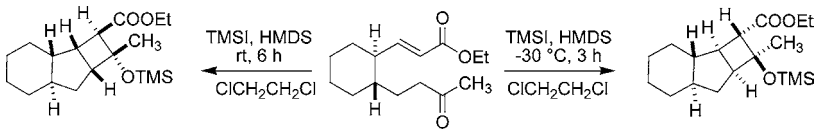
ABSTRACT



The tandem intramolecular Michael-aldol reaction was studied as a tool for the construction of the C-ring of hexacyclinic acid. By changing the reaction conditions it was possible to selectively obtain either the kinetic or the thermodynamic product. Retro-aldol reaction and subsequent epimerization provides four individual cyclopentane derivatives that can be incorporated as building blocks in natural product syntheses.

Hexacyclinic acid (**1**), a polyketide produced by *Streptomyces* cellulosae subsp. griserubiginosus (strain S1013), was isolated in 2000 by Zeeck and co-workers.[1] It exhibits similar structural features compared to (−)-FR182877 (**2**) isolated in 1998 from *Streptomyces* sp. No. 9885 by Fujisawa Pharmaceutical Company.[2] (−)-FR182877 (WS 9885B, *Cyclostreptin*) has attracted broad scientific interest due to its potent cytotoxic activity.[3] Consequently, biomimetic total syntheses of (−)-FR182877[4b−d] and its enantiomer[4a] have been described by the groups of Evans and Sorensen.

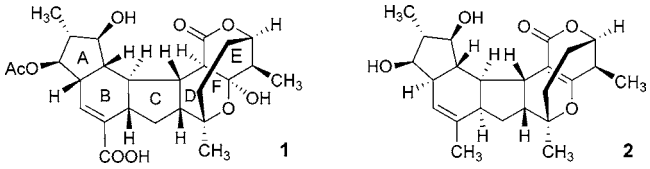


Figure 1. Hexacyclinic acid (**1**) and (−)-FR 182877 (**2**).

Even though no total synthesis of hexacyclinic acid has been put forward, the complex structure combined with its biological activity has initiated several partial syntheses.[5,6] We have published the synthesis of the ABC fragment of hexacyclinic acid[6] employing an intramolecular Diels−Alder reaction followed by a tandem intramolecular Michael-aldol reaction[7] as the pivotal steps to furnish **4** (Scheme 1). It was obtained as an inseparable mixture of diastereomers, making

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(1) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258−3261.

(2) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123−130.

(3) Edler, M. C.; Buey, R. M.; Gussio, R.; Marcus, A. I.; Vanderwal, C. D.; Sorensen, E. J.; Diaz, J. F.; Giannakakou, P.; Hamel, E. *Biochemistry* **2005**, *44*, 11525−11538.

(4) (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553. (b) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393−5407. (c) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787−1790. (d) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531−13540.

(5) (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560−1561. (b) Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron Lett.* **2004**, *45*, 927−929. (c) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221−4224. (d) Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron* **2005**, *61*, 2335−2351. (e) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985−7995. (f) Funel, J.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555−4558. (g) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223−4226.

(6) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889−3892.

(7) (a) Ihara, M.; Ohnishi, M.; Takano, M.; Makita, K.; Taniguchi, N.; Fukumoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 4408−4410. (b) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107−8115. (c) Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 8092−8100. (d) Ihara, M.; Taniguchi, T.; Yamada, M.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 8071−8074. (e) Takasu, K.; Ueno, M.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 2145−2148.

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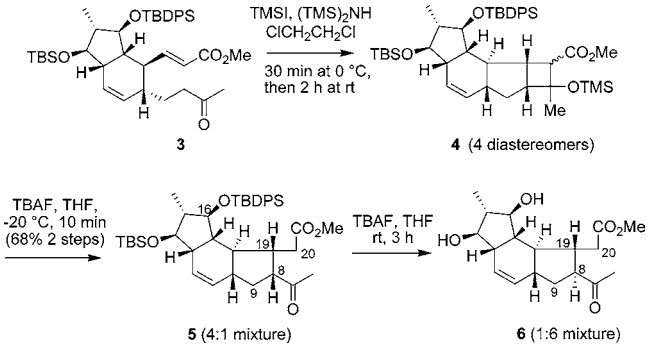
Scheme 1. Construction of the C-Ring



it difficult to determine the configuration of the major isomer. The retro-aldol reaction proceeded when **4** was treated with TBAF to give the methyl ketone **5** as a 4:1 diastereomeric mixture. It was stated that the NOESY cross-peak between H20 and H16 supports the configuration at C19, on the other hand configurational assignment at C8 was just based on coupling constants between H8 and H9.[6]

When **5** was subjected to the action of TBAF (THF, rt, 3 h), total deprotection took place. The diol **6** was obtained as a 6:1 mixture of diastereomers. Fortunately, diol **6** was crystalline and we were able to obtain an X-ray structure. According to the X-ray analysis (Figure 2), eight out of nine

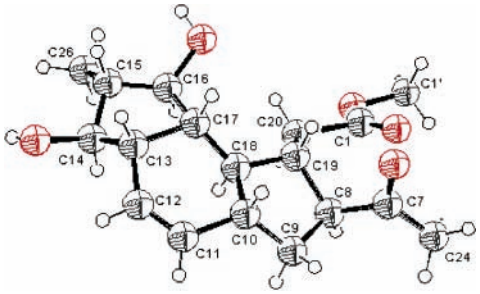


Figure 2. X-ray structure of **6**.

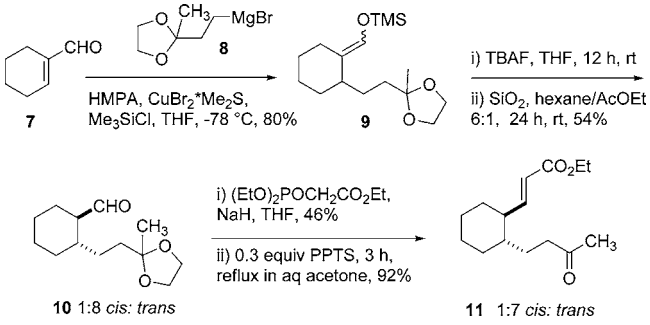
stereocenters were constructed correctly, leaving only the configuration at C8 to be opposite that of the natural product.

Formation of a trans-fused cyclobutane derivative as the product of the tandem Michael-aldol reaction could be an explanation for the configuration at C8, but also epimerization under basic deprotection conditions (4 equiv of TBAF, THF, rt) could serve as a rational.

To understand the stereochemical outcome of the tandem Michael-aldol reaction and to establish the conditions of the retro-aldol reaction that avoid epimerization, we studied these transformations on a readily available substrate (**11**) (Scheme 2).

Methyl ketone **11** was synthesized in 5 steps starting from cyclohexene-1-carbaldehyde (**7**) through a conjugate addi-

Scheme 2. The Synthesis of Model Compound **11**



tion[8,9] of **8**[10] to aldehyde **7**. Silyl ether **9** was treated with TBAF to give aldehyde **10**, which was subjected to equilibration by using SiO_2 in hexane−AcOEt (6:1 v/v) at room temperature to establish the desired trans-substituted cyclohexane derivative with 8:1 selectivity. Subsequently, the α,β unsaturated ester was introduced according to the Horner−Emmons protocol. The 1,3-dioxolane protecting group was removed in refluxing aqueous acetone with 0.3 equiv of PPTS to provide methyl ketone **11** as a mixture of cis and trans diastereomers (1:7) which were separated by HPLC.[11]

Having **11** in hand, the diastereoselectivity of the tandem Michael-aldol reaction was studied as summarized in Table 1 (Scheme 3).

Table 1. TMSI-HMDS Mediated Tandem Michael-Aldol Reaction

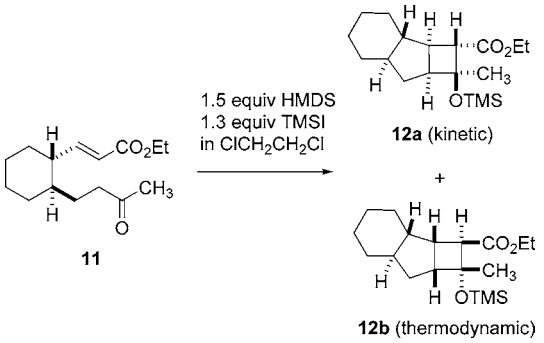
entry	conditions[b]	diastereomeric ratio **12a**:**12b**[c]	yield (%)[d]
1	rt, 6 h	1.0:17.5	78
2	rt, 3 h	1.0:14.3	79
3	rt, 60 min	1.0:4.4	82
4	rt, 10 min	1.8:1.0	87[a]
5	0 °C, 6 h	1.0:1.7	77[a]
6	0 °C, 3 h	1.5:1.0	82[a]
7	0 °C, 60 min	5.4:1.0	81[a]
8	0 °C, 10 min	8.2:1.0	83[a]
9	−20 °C, 6 h	8.2:1.0	70[a]
10	−20 °C, 60 min	12.4:1.0	81[a]
11	−20 °C, 10 min	16.2:1.0	49[a]
12	−30 °C, 3 h	16.2:1.0	79[a]
13	−30 °C, 60 min	17.6:1.0	71[a]

[a] Incomplete reaction. [b] For all entries in Table 1 the concentration of **11** was 0.1 M. [c] Diastereomeric ratio was determined by GC. Other products were also detected (up to 6), but not listed in Table 1. Analysis was done on crude products. The composition of crude products (**12**) was also controlled by the intensity of the signals corresponding to the $OSi(CH_3)_3$ group (δ 0.26−0.15 ppm) in ^1H NMR spectra (in C_6D_6). [d] For the mixture of diastereomers after chromatographic purification (hexanes−EtOAc (50:1 v/v), R_f 0.10−0.15).

When the reaction was carried out at 0, −20, or −30 °C compound **12a** was obtained as the major product. On the

(8) Takakis, I. M.; Tsantali G. G. *J. Org. Chem.* **2003**, *68*, 6455−6458.
(9) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025−4028. (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986,** *27*, 4029−4032.
(10) Büchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122−1123.
(11) See the Supporting Information for details on the HPLC separation of **11**.

Scheme 3. Tandem Michael-Aldol Reaction



other hand, when the reaction was performed at room temperature for more than 1 h, product (**12b**) was formed selectively. In general, longer reaction times favor the *thermodynamic* product with better yields, whereas shorter reaction times favor the *kinetic* product (Table 1).

Both **12a** and **12b** were isolated and analyzed with nOe experiments to assign their relative stereochemistry.

NOESY spectra of **12a** support the structure shown in Figure 3 with cis-fusion between the cyclopentane and the

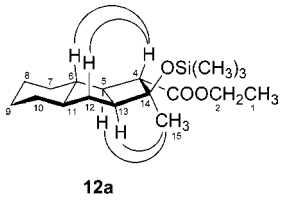


Figure 3. Assignment of the relative stereochemistry of the kinetic product (**12a**) with the help of NOESY NMR experiment.

cyclobutane rings and trans-orientation between H5 and H6 as in hexacyclinic acid.

In the case of the **12b**, a nOe between H4 and H11 is a strong argument to support the proposed structure (Figure 4).

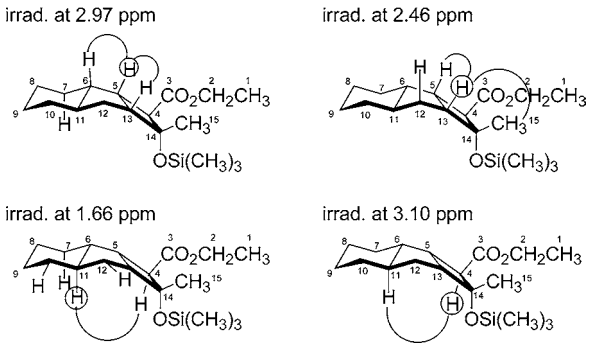
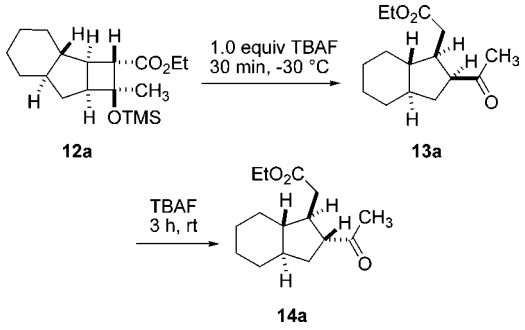


Figure 4. Assignment of the relative stereochemistry of the thermodynamic product (**12b**) with nOe experiments.

Scheme 4. Reaction of **12a** with TBAF



With **12a** in hand we performed the retro-aldol reaction putting our particular focus on the potential epimerization at C8.

When **12a** was treated with TBAF (1.0 equiv, −30 °C, 30 min), the corresponding methyl ketone **13a** was obtained in 80% yield (Scheme 4) as indicated by NOESY experiments (Figure 5).

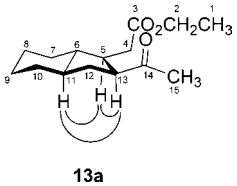


Figure 5. Configurational assignment of **13a** by NOESY.

When methyl ketone **13a** was additionally treated with TBAF at room temperature (Scheme 4), epimerized compound **14a** was isolated as the sole product and analyzed by nOe experiments (Figure 6).

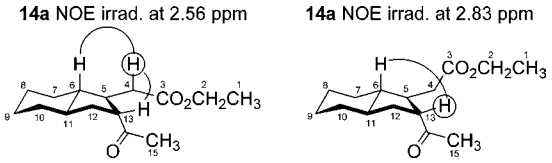
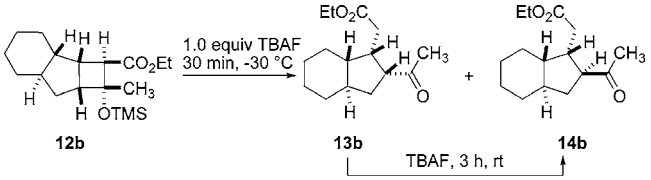


Figure 6. Assignment of the relative configuration of **14a** with nOe experiments.

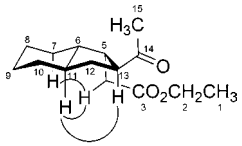
When **12b** was treated with TBAF over 30 min at −30 °C, a 2.8:1 diastereomeric mixture of two methyl ketones **13b** and **14b** was isolated. After treatment of this diastereomeric mixture with TBAF at room temperature (3 equiv, 3 h), only isomer **14b** could be isolated (Scheme 5).

The structure of **14b** was studied with the help of ROESY (Figure 7).

Scheme 5. Reaction of **12b** with TBAF



With the results obtained, we can now explain the unexpected epimerization at the C8 center of **5** under conditions of silyl deprotection with TBAF and provide a reliable path for the further elaboration of the total synthesis of hexacyclinic acid. Additionally, we provided a method that allows the synthesis of diastereomeric derivatives of hexacyclinic acid as well as the diastereoselective synthesis of other 1,2-disubstituted octahydroindene derivatives, with four diastereomers accessible through either the kinetic or thermodynamic product and subsequent epimerization.



14b

Figure 7. Assignment of the configuration of 1**4b** by ROESY experiment.

Acknowledgment. This work was financially supported by the DFG.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **9**, **10**, **11**, **12a**, **12b**, **13a**, **14a**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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