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Stereoselective Synthesis of Pyridinones: Application to the Synthesis of (−)-Barrenazines

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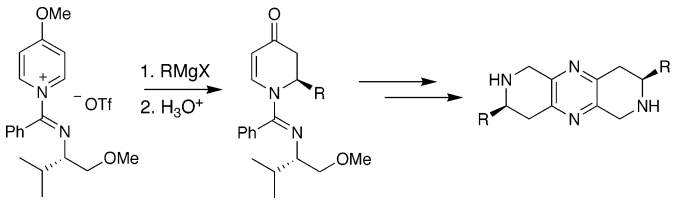
ABSTRACT



The stereoselective synthesis of pyridinones was accomplished by the nucleophilic addition of Grignard reagents to a chiral pyridinium salt derived from 4-methoxypyridine. This methodology was applied to an expedient synthesis of (−)-barrenazine A and B. After N-functionalization and 1,4-reduction of the pyridinone system, the corresponding α-amino piperidinones readily undergo dimerization to give the hexahydrodipyridinopyrazine skeleton of the barrenazine alkaloids.

In 2003, Kashman and co-workers isolated two novel cytotoxic alkaloids, barrenazine A (**1**) and B (**2**), from an unidentified tunicate collected at Barren Islands in Madagascar.[1] These two compounds have a unique 1,3,4,6,8,9-hexahydrodipyridino[3,4-*b*:3′,4′-*e*]pyrazine skeleton. Related naturally occurring structures are rare, and among those are the hexahydrodipyranopyrazines palythazin and isopalythazine[2c] and the trihydropyranopyrazine clavulazine.[2a] A synthesis of palythazine in six steps was reported starting from tetra-O-benzoylated D-glucose.[2b] Herein, we report an expedient, enantioselective synthesis of both barrenazines from a common intermediate.

Our retrosynthetic analysis of barrenazines A and B is depicted in Figure 1. It was envisioned that the pyrazine core could be assembled through the dimerization of amino pyridinone **3**. Fragment **3** would be elaborated by the stereoselective functionalization of 4-methoxypyridine (**4**).

A strategy that has been frequently used to prepare substituted piperidine and piperidinone alkaloids[3] consists of the addition of a nucleophile to a chiral or achiral *N*-alkyl- or *N*-acylpyridinium salt.[4] As part of our ongoing research program directed toward the expedient synthesis of enantiopure, polysubstituted piperidines from readily available starting materials, we developed a new methodology for the generation of pyridinium salts from pyridine, secondary amide **5**, and triflic anhydride.[5] These salts undergo highly diastereo- and regioselective addition of carbon nucleophiles to produce dihydropyridines.

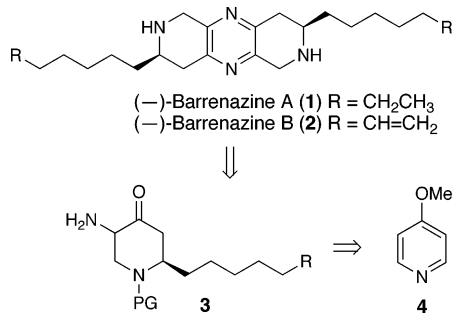


Figure 1. Retrosynthetic analysis of barrenazine A and B.

(1) Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433−2435.
(2) (a) Watanabe, K.; Iguchi, K.; Fujimori, K. *Heterocycles* **1998**, *49*, 269−274. (b) Jarglis, P.; Lichtenthaler, F. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 141−142. (c) Uemura, D.; Toya, Y.; Watanabe, I.; Hirata, Y. *Chem. Lett.* **1979**, *12*, 1481−1482.

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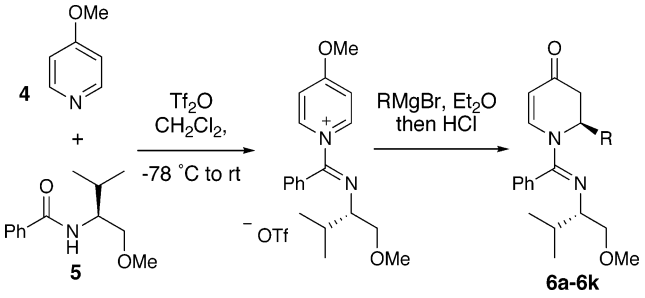
The addition of 4-methoxypyridine (**4**, 2.3 equiv) to a mixture of amide **5** (1.0 equiv) and triflic anhydride (1.1 equiv) at −78 °C led to the formation of the desired pyridinium salt (Table 1).

Table 1. Nucleophilic Addition to Pyridinium Salts Derived from 4-Methoxypyridine (**4**) and Amide **5**



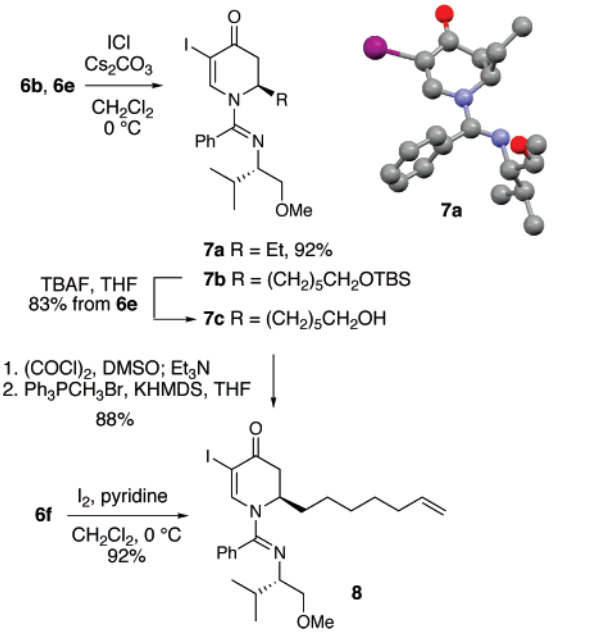
entry	RMgBr	product	yield (%)[a]	dr[b]
1	Me	**6a**	85	95:5
2	Et	**6b**	76	93:7
3	*n*-Bu	**6c**	71	>95:5
4	*t*-Bu	**6d**	61	93:7
5	$(CH_2)_6OTBS$	**6e**	70	>95:5
6	$(CH_2)_5CH{=}CH_2$	**6f**	84[c]	93:7
7	$CH{=}CH_2$	**6g**	64	92:8
8	$C{\equiv}CCH_3$	**6h**	52 + 8	83:17
9	$C{\equiv}CPh$	**6i**	65	89:11
10	Ph	**6j**	66	91:9
11	furanyl	**6k**	65	95:5

[a] Products isolated as a single diastereomer. [b] Determined by ^1H NMR of the crude product. [c] Mixture of diastereomers (dr = 13:1).

NMR monitoring of the pyridinium salt formation[6] indicated that the activation process was complete within 5 h at room temperature. The pyridinium salt solution was then cooled to −20 °C, and an ether solution of the Grignard reagent was added. After acidic hydrolysis of the intermediate methyl enol ethers, pyridinones **6a**−**k** were obtained in excellent diastereoselectivities and good yields.[7] We found that using THF as a cosolvent in the reaction led to a decrease in diastereoselectivity.[8] The addition proceeded well not only with simple alkylmagnesium reagents such as methylmagnesium bromide (entry 1) but also with bulkier nucleophiles such as *tert*-butylmagnesium bromide (entry 4). Furthermore, the addition of vinyl-, aryl-, and furylmagnesium bromides led to adducts **6g**, **6j**, and **6k**, respectively, with excellent stereocontrol (entries 7, 10, and 11). Only the addition of alkynylmagnesium reagents resulted in a lower selectivity (entries 8 and 9).[9]

The synthesis of (−)-barrenazines A and B started with the introduction of the side chain using an appropriate organomagnesium reagent (Scheme 1). Two approaches were pursued in parallel starting from **6e** (Table 1, entry 5) and from **6f** (Table 1, entry 6).

Scheme 1. Synthesis of α-Iodo Pyridinone **8** and Crystal Structure of **7a**



The α-iodination of pyridinone **6e** as well as that of ethyl derivative **6b** were efficiently performed using ICl in the presence of Cs_2CO_3 to give **7a** and **7b**, respectively.[10] The generation of the unsaturated side chain of (−)-barrenazine B (**2**) was completed by desilylation using TBAF, Swern oxidation, and Wittig olefination to give **8**.

Alternatively, the terminal olefin moiety of (−)-barrenazine B (**2**) could be directly introduced when using the organomagnesium reagent derived from 7-iodohept-1-ene. Thus, the corresponding pyridinone **6f** was obtained in high diastereoselectivity (Table 1, entry 6). The chemoselective

(3) For recent reviews on the stereoselective synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989.

(4) For selected, recent references on the syntheses of pyridinones by addition of nucleophiles to pyridinium salts and the use of pyridinones in synthesis, see: (a) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227−5228. (b) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. *Org. Lett.* **2005**, *7*, 5059−5062. (c) Knapp, S.; Yang, C.; Pabbaraja, S.; Rempel, B.; Reid, S.; Withers, S. G. *J. Org. Chem.* **2005**, *70*, 7715−7720. (d) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219−5231. (e) Ege, M.; Wanner, K. T. *Org. Lett.* **2004**, *6*, 3553−3556. (f) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863−2866.

(5) (a) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747−2750. (b) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368−2371. (c) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520. (d) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.

(6) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694−1703.

(7) See Supporting Information for details.

(8) The organomagnesium reagents were either purchased as solutions in Et_2O or freshly prepared prior to use from the corresponding alkyl iodides, vinyl, or phenyl bromides using *t*-BuLi or by deprotonation using *n*-BuLi, followed by transmetalation to $MgBr_2{\cdot}OEt_2$. See Supporting Information for details.

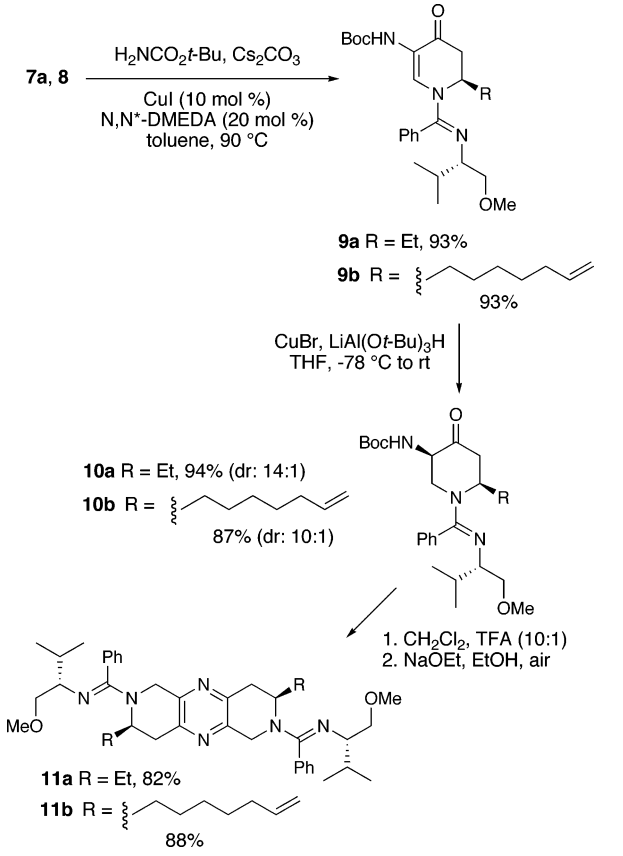
(9) THF had to be added in these reactions to solubilize the organomagnesium reagents.

(10) ICl for iodination of pyridinones: (a) Comins, D. L.; Hiebel, A.-C.; Huang, S. *Org. Lett.* **2001**, *3*, 769−771. (b) See also: Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141−9144.

conversion of **6f** to **8** was then accomplished using I_2 in the presence of pyridine.[11]

α-Iodo, α,β-unsaturated carbonyl compounds are valuable intermediates in organic synthesis, especially in transition-metal-mediated reactions.[12] For the purpose of the synthesis of **1** and **2**, α-iodo **7a** and **8** were transformed into the Boc-amino enones **9a**,**b** via a Buchwald's Cu-catalyzed C−N cross-coupling using *tert*-butyl carbamate[13] (Scheme 2).

Scheme 2. Synthesis of Protected Barrenazine A and B



Originally, we intended to use **9** directly in a reductive cyclization to construct the pyrazine core of barrenazine. However, the α-amino enone obtained from **9a** upon TFA deprotection did not undergo the desired reaction using Pd/C and hydrogen gas.[14] Presumably, the enone system is too deactivated because of conjugation of the free amino group with the amidine moiety. It was anticipated that reduction of the Boc derivatives **9** to the saturated piperidinone **10** would circumvent this problem. The construction of symmetrical pyrazines from α-amino aldehydes and ketones is well-known, and condensation usually proceeds fairly easily.[15] The 1,4-reduction of **9** using known procedures such as L-selectride[16] or Stryker's reagent proved to be difficult.[17] Poor selectivity of 1,4- vs 1,2-reduction and/or low yields of the corresponding piperidinones were observed. The only reagent that gave complete 1,4-selectivity and full conversion was a combination of CuBr and $LiAl(O^tBu)_3H$.[18] Thus, we could obtain compounds **10a** and **10b** in excellent yields and good diastereoselectivities. Although having diastereomerically enriched **10** is meaningless for the remainder of the synthesis, as the stereogenic center is lost in the subsequent step, the Boc-amino ketones **10** are interesting chiral building blocks.

The configuration of piperidinone **10a** was determined by analyzing the coupling constants and by NOESY experiments. Nitrogen heterocycles protected with acyl, carbamate, or imidate groups are known to place substituents at the 2-position axially, to minimize $A^{1,3}$ strain (Figure 2).[19] NMR

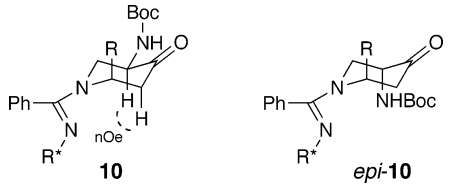


Figure 2. Configuration of *N*-Boc-amino ketone **10**.

analysis indicated that diastereomer **10** was the major product arising from the reduction (Figure 2).

Having Boc-amino ketones **10** in hand, the next steps consisted of the amine deprotection with TFA followed by the oxidative cyclization under basic conditions in air to afford **11**.

The amidine auxiliary was then removed via an intramolecular, alkoxy-assisted strategy using BBr_3 (Scheme 3).

(11) I_2/pyridine reagent: (a) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263−1266. (b) Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568−6570. (c) Johnson, C. R.; Adam, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917−918.

(12) For review of β-iodo carbonyl compounds in Pd-catalyzed cross-coupling reactions, see: Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179−194.

(13) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669.

(14) For cyclizations of β-amino cyclohexenones, see: (a) Drögemüller, M.; Flessner, T.; Jautelat, R.; Scholz, U.; Winterfeldt, E. *Eur. J. Org. Chem.* **1998**, *2811*, 1−2831. (b) Kramer, A.; Ullmann, U.; Winterfeldt, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2865−2867.

(15) Selected examples: (a) Tonsiengsom, F.; Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Synthesis* **2005**, in print. (b) Gosh, U.; Ganessunker, D.; Sattigeri, V. J.; Carlson, K. E.; Mortensen, D. J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2003**, *11*, 629−657. (c) Chiba, T.; Sakagami, H.; Murata, M.; Okimoto, M. *J. Org. Chem.* **1995**, *60*, 6764−6770.

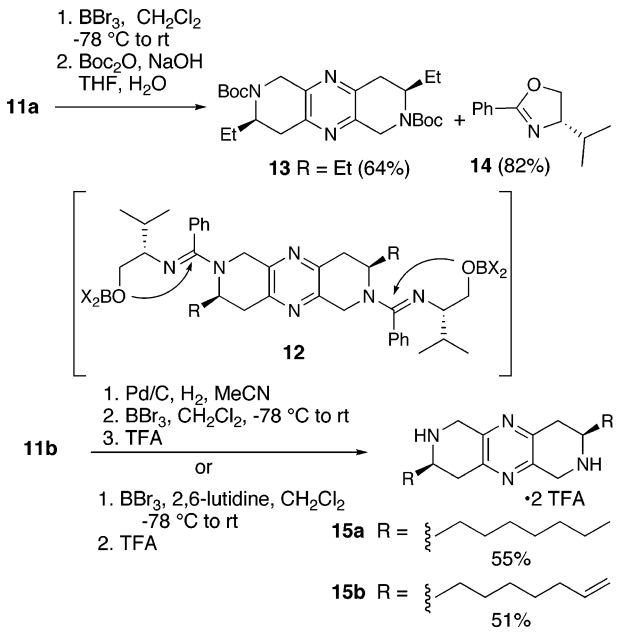
(16) Selected examples: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem.−Eur. J.* **2003**, *9*, 3415−3426. (b) Tasber, E. S.; Garbaccio, R. M. *Tetrahedron Lett.* **2003**, *44*, 9185−9188. (c) Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, *3*, 711−714. (d) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184−2185.

(17) Selected examples: (a) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. P.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779−2788. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627−4630. (c) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293.

(18) 1,4-Reduction of enones with CuX/LiAlH: (a) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053−5056. (b) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1984**, *49*, 3392−3394. (c) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180−3188.

(19) (a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681. (b) Hoffmann, H. R. *Chem. Rev.* **1989**, *89*, 1841−1860. (c) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413. See also the X-ray crystal structures in the Supporting Information.

Scheme 3. Amidine Group Cleavage and Isolation of Barrenazine A (**15a**) and B (**15b**) Bis(trifluoroacetate)[a]



[a] TFA salts were obtained after HPLC purification; see Supporting Information for details.

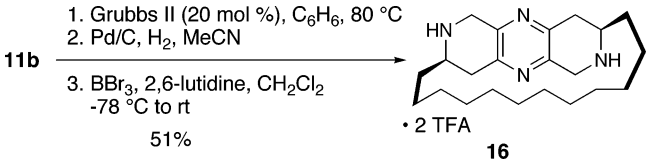
After cleavage of the methoxy groups on the amidine moiety of **11a**, **12** spontaneously fragmented to afford oxazoline **14** and free hexahydrodipyridinopyrazine, which was isolated as its Boc derivative **13**. The same procedure applied to pyrazine **11b**, obtained after hydrogenation of the terminal alkenes, produced barrenazine A bis(trifluoroacetate) (**15a**) in 55% yield.

The amidine cleavage with the unsaturated side chain still in place proved to be more challenging. A mixture with varying amounts of brominated side chains was observed if the same reaction conditions as before were used. Fortunately, a combination of BBr_3 and 2,6-lutidine turned out to cleave the methoxy groups efficiently while leaving the terminal olefin untouched. Thus, barrenazine B (**15b**) was isolated as its bis(trifluoroacetate) salt in 51% yield.[20] The spectroscopic data for both **15a** and **15b** were identical to those reported by Kashman.[1] Neutralization upon treatment with saturated aqueous $NaHCO_3$ led to barrenazine A and B.

(20) The ratio of barrenazine/TFA was determined by NMR using α,α,α-trifluorotoluene as the internal standard.

Pyrazine **11b** is an interesting compound to apply ring-closing metathesis conditions.[21] Applying Grubbs' second generation catalyst, followed by hydrogenation of the double bond and removal of the chiral auxiliary, allowed the isolation of the cyclophane-type macrocycle **16** in 51% yield (Scheme 4).[22]

Scheme 4. RCM of **11b** to Give Cyclophane **16**[a]



[a] TFA salt was obtained after HPLC purification; see Supporting Information for details.

In summary, an expedient synthesis of (−)-barrenazine A and B was accomplished in 30% (eight steps) and 28% (seven steps) overall yield, respectively, from 4-methoxypyridine. The synthetic route allows for the preparation of various analogues as exemplified by the synthesis of the ethyl side chain analogue.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds and crystal structure data for **6i** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For reviews on the olefin metathesis reaction, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (c) Connor, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(22) A mixture of *E*/*Z* double-bond isomers in a ratio of 8:1 is isolated, if the hydrogenation step is avoided.