COMMUNICATIONS

GHEORGHE SURPATEANU, ALAIN LABLACHE-COMBIER, PIERRE
GRANDCLAUDON, and BERNARD MOUCHEL. Cycloaddition
Reaction of 1,2,4-Triazolium Phenacylides with Cinnamic Esters.......863

ISTVÁN BITTER, GÁBOR TÓTH, ISTVÁN HERMECZ, and ZOLTÁN
MÉSZÁROS. Nitrogen Bridgehead Compounds Part 59. Nucleophilic
Substitution Reactions of 9-Bromo-6,7,8,9-tetrahydro-4H-pyrido-
[1,2-a]pyrimidin-4-ones........................................869

YASUOKI MURAKAMI, YUUSAKU YOKOYAMA, CHIYOKO AOKI,
CHIEMI MIYAGI, TOSHIKO WATANABE, and TAICHI OHMOTO.
A New Route to 4-Oxygenated β-Carbolines: The Total Synthesis
of Crenatine.........................................................875

HANH DUFAT-TRINH VAN, ELISABETH SEGUIN, FRANÇOIS TILLEQUIN,
and MICHEL KOCH. Total Synthesis of 7-Hydroxy-”9-oxa”-anthra-
cyclinone and Glycoside Derivatives ................................879

SHIZUAKI MURATA, TAKASHI SUGimoto, and SADAO MATSUURA.
A Novel Ring Formation of 1,2-Dihydroquinoxalines .................883

HANS LUDESCHER, CHING-PONG MAK, GERHARD SCHULZ, and
HANS FLIRI. Chemistry of Penicillin Diazoketones. Part II: From
Beta-lactam to Beta-lactone .........................................885

MASANORI SOMEI, FUMIO YAMADA, and YOSHIHIKO MAKITA.
Total Syntheses of (±)-Agroclavine-I, (±)-6-Nor-chanoclavine-II,
and (±)-Chanoclavine-II............................................895

MONA HASSAN MOHAMED, NADIA SOBHY IBRAHIM, and MOHAMED
HILMY ELNAGDI. Nitriles in Heterocyclic Synthesis: Synthesis of
Some New Pyridine, Pyridazine and Pyrimidine Derivatives.........899

EBTISAM ABDEL AZIZ HAFEZ, MOHAMED HILMY ELNAGDI, ABDEL
GHANI ALI ELAGAMEY, and FATHY MOHAMED ABDEL AZIZ
EL-TAWEEL. Nitriles in Heterocyclic Synthesis: Novel Synthesis of
Benzo[c]coumarin and of Benzo[c]pyran[3,2-c]quinoline Derivatives....903

JUZO NAKAYAMA, MASAHIRO SHIBUYA, and MASAMATSU HOSHINO.
Preparation of 2,5-Diacylselenophenes by Condensation of \(\alpha,\alpha'-\)Diketo Selenides with Glyoxal

MASAKATSU MATSUMOTO and NOBUKO WATANABE. A Facile Synthesis of 4-Mercaptoindoles

KLAUS TH. WANNER and ANNEROSE KÄRTNER. Isomerization of \(N\)-Acyl-1,2,5,6-tetrahydropyridines to \(N\)-Acyl-enamines by Palladium on Carbon

KLAUS TH. WANNER and ANNEROSE KÄRTNER. Asymmetric \(\alpha\)-Amidoalkylation. Synthesis of \(\alpha\)-Substituted Piperidines of High Enantiomeric Purity

JUNKO KOYAMA, TERUYO OKATANI, KIYOSHI TAGAHARA, YUKIO SUZUTA, and HIROSHI IRIE. Synthesis of Guaipyridine, Epiguai-pyridine, and Related Compounds

MAKOTO WADA, HIDEKI AIURA, and KIN-YA AKIBA. Synthesis of Pyrrolidine Derivatives by Improved Aminoselenation via Addition of Boron Trifluoride Complex of Dihomoallylcuprate to Aldimines Containing \(\alpha\)-Hydrogen

YOSHITERU OSHIMA, MAKI OKAMOTO, and HIROSHI HIKINO. Epimedins A, B and C, Flavonoid Glycosides of \(Epimedium koreanum\) Herbs

JUZO NAKAYAMA, YOICHI NAKAMURA, SHIGERU MURABAYASHI, and MASAMATSU HOSHINO. Preparation of \(\alpha\)-Quinque- and \(\alpha\)-Septithiophenes and Their Positional Isomers

YANG-CHANG WU, TIAN-SHUNG WU, MASATAKE NIWA, SHENG-TEH LU, and YOSHIMASA HIRATA. Thalic sessine, a New \(C_{20}\)-Diterpenoid Alkaloid from \(Thalictrum sessile\) Hayata

HETEROCYCLIC PAPERS

LAJOS KOVÁCS, PÁL HERCZEGH, GYULA BATTA, and ISTVÁN FARKAS. Two Acyclic Analogues of 2-\(\beta\)-D-Ribofuranosylthiazole-4-carboxamide (Tiazofurin)

GURY ZVILICHOVSKY and MORDECHAI DAVID. Molecular Structure and Stability of Isoxazolium Enolates

SHARON MARINUZZI-BROSEMER, BHALCHANDRA H. PATWARDHAN, KENNETH A. GREENBERG, and DONALD C. DITTMER. Interaction of Thiethes with Electron-deficient Molecules

JOSÉ M. ALONSO, M. ROSARIO MARTÍN, JAVIER DE MENDOZA, TOMÁS TORRES, and JOSÉ ELGUERO. Proton-ionizable Macrocycles Containing 1,2,4-Triazole and 4-Amino-1,2,4-triazole Subunits

CHING-PONG MAK, GERHARD SCHULZ, and HANS FLIRI. Chemistry of Penicillin Diazoketones. Part III: Transformation of Tricyclic Beta-lactams
ASYMMETRIC α-AMIDOALKYLATION.
SYNTHESIS OF α-SUBSTITUTED PIPERIDINES OF HIGH ENANTIOMERIC PURITY

Klaus Th. Wanner* and Annerose Kärtner
Institut für Pharmazie und Lebensmittelchemie der Universität München,
Sophienstr. 10, 8000 München 2, FRG

Abstract - A stereoselective α-amidoalkylation was performed employing the chiral and cyclic enamide I. The resulting amides were employed in the synthesis of the title products.

Designing highly efficient methods for asymmetric synthesis constitutes one of the most challenging and exciting problems in synthetic organic chemistry and there is an unabating search for new enantio- and diastereoselective bond forming reactions. Most of the well established methods comprise the reaction of chiral nucleophiles such as enolates, wherein the chirality stems from a chiral auxiliary, with achiral electrophiles. In contrast thereto reactions of electrophilic equivalents provided with a chiral auxiliary are few and have appeared in the literature only recently. We have designed a novel asymmetric synthesis based on the concept of α-amidoalkylation which in general is accomplished by trapping an electrophilic N-acyliminium ion (e.g. I) with a nucleophile. It occurred to us that a chiral appendix adjacent to the iminium subunit in I could favour the approach of a nucleophile along one path (either A or B) resulting in a stereoselective bond formation. Subsequent removal of the chiral auxiliary would then afford substituted piperidines in optically active form.

In this letter we wish to report the successful implementation of this plan. Enamides can act as α-amidoalkylation agents and therefore I, which is readily available even in 20 g quantities by catalytic isomerization, seemed best suited for our purposes. Indeed I could be coupled with various silyl enolethers (4) to give a mixture of the diastereomeric α-substituted amides and 6.
The transformation was effected by adding 1 in CH₂Cl₂ to a solution of HCl in CH₂Cl₂ at -78°C, stripping off excess HCl, treating the remaining solution with TiCl₄ or SnCl₄ (1.05 eq, 0.5 h) and subsequent addition of the respective enol ether 4 (1.25-2.0 eq, 0.5-1.0 h, -78°C). Aqueous workup then yielded a residue containing almost exclusively the desired amidoalkylation products 5 and 6 (as established by TLC) beside some ketone resulting from silyl enol ether hydrolysis.

We assume that the reaction proceeds via the α-chloroamide 2 and the iminium ion 3 having the indicated structures. The stereoselectivity of the bond forming reaction was determined by HPLC and ranged from a modest 35.3:64.7 ratio (entry 1) to a quite reasonable 6.2:93.8 ratio when the sterically demanding enolether 4c was applied (entry 4).

<table>
<thead>
<tr>
<th>Table</th>
<th>Lewis-Acid</th>
<th>Enol ether</th>
<th>Ratio</th>
<th>α-Subst. Amide 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>entry</td>
<td>4</td>
<td>R¹</td>
<td>R²</td>
<td>5/6²</td>
</tr>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>a</td>
<td>H</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>a</td>
<td>H</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>3</td>
<td>TiCl₄</td>
<td>b</td>
<td>H</td>
<td>C(CH₃)₃</td>
</tr>
<tr>
<td>4</td>
<td>TiCl₄</td>
<td>c</td>
<td>CH₃</td>
<td>C₆H₅</td>
</tr>
</tbody>
</table>

a) Determined by HPLC on a LiChrosorb Si 60 column eluted with 10-20% EtOAc in hexane. b) Yield of pure diastereomer 6, from flash or radial chromatography. c) Specific rotation (c=1.0 in CH₃OH). d) Not determined. e) The absolute configuration of the newly produced asymmetric center is presently unknown. However, it is reasonably expected that the major product belongs to (R)-series (6c), by taking into account the results obtained with 4a,b.
In each case the major diastereomer could be separated from its epimer by chromatography and subsequent crystallisation. The compounds 6a-c are valuable intermediates in the synthesis of enantiomerically pure piperidine derivatives. This is best demonstrated by their transformation to sedamine 10, a piperidine alkaloid of the sedamine family, homopipecolic acid 12 and the phenacylpiperidine 13 as outlined below. Said reactions also enabled us to assign the configuration for the newly created stereocenter at C-2 in some cases.

Scheme 2

Reduction of the amide 6a with LiAlH4 (0.5 eq., Et2O: THF = 80:1, 1.5 h, -78°C) occurred in a notably stereoselective manner, yielding the alcohol 7 as the major product along with the minor isomer 8 in a 91.5: 8.5 ratio. The epimer 7 was readily separated from 8 by chromatography (83.7% yield) and cleaved to the aminoalcohol 9 (90.1% yield; \([\alpha]_{D}^{28}= +32.0\degree, c=2.03, CH_3OH) using 0.5 M KOH in CH3OH and heating to reflux for 18 h. Methylation of 9 (CH2O, 2.5 eq. NaCNBH3) followed by chromatography afforded optically pure (+)-sedamine (10) in 93.0% yield. The physical data of the piperidine alkaloid 10 were in good accord with those of the natural 2S,8S-(-)-sedamine, except for the sign of specific rotation (2S,8S-(-)-sedamine: \([\alpha]_{D}^{29}= -82.4\degree, c=5.0, CH_3OH); 10: [\alpha]_{D}^{29}= +92.9\degree, c=1.0, CH_3OH) indicating that the major product (6a) from the amidooalkylation has 2R-configuration.

In order to synthesize homopipecolic acid (12), 7a was subjected to a Baeyer Villiger oxidation (3 eq. CF3CO2H, 0–20°C, 1 h) which afforded the N-protected amino acid 11 (87.6% yield). Treatment of the amide 11 with 1.5 M H2SO4 (4h, 95°C) furnished after chromatography pure R-(-)-homopipecolic acid (12) in 90.6% yield. The R stereochemistry has been established by a comparison of the specific rotation of 12 (\([\alpha]_{D}^{29}= -36.9\degree, c=0.37, H_2O) with reported literature values (R: \([\alpha]_{D}^{29}= -24\degree, c=0.4, H_2O; S: \[\alpha]_{D}^{29}= +29\degree, c=1.0, H_2O). Finally 6c was converted to the aminoketone 13 in 61.6% isolated yield by the action of HCl/CH3OH (25°C, 72h; [\alpha]_{D}^{29}= +9.9\degree, c=1.8, CH3OH).
In order to unequivocally verify that no racemization had occurred during hydrolysis (6c- 13 and 11-12) a sample of each 13 and 12 was treated with (-)-camphanic acid chloride. 6c and 11 were formed each as a single diastereomer indicating that the piperidine derivatives (12 and 13) were virtually enantiomerically pure.

In summary we have developed a method for the asymmetric amidoalkylation mediated by a chiral enamide (1) and demonstrated its utility in the synthesis of α-substituted piperidines of high enantiomeric purity. Currently we are engaged in further expand the scope of the reaction.

ACKNOWLEDGEMENT
We are greatly indebted to Prof. F. Eiden for generous support. We also thank Dr. S. Jendrzejewski for NMR measurements.

REFERENCES AND FOOTNOTES

(2) See ref. 1, Vol. 2 p 243 and Vol. 3 pp 1-341.
(5) See the preceding letter.
(6) Satisfactory spectroscopic data (1H-NMR, JR, MS) and elemental analyses were obtained for the compounds reported in this paper.
(8) Calculated from [α] 546 and [α] 578°.
(10) Determined by HPLC (5c/6c) and 360 MHz 1H-NMR(11). A control experiment had revealed that the 1H-NMR signals of 11 and its epimer derived from 5b can clearly be resolved.