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Photocyclization of 2-Azabicyclo[3.3.0]octane-3-carboxylate Derivatives: Induced and Noninduced Diastereoselectivity

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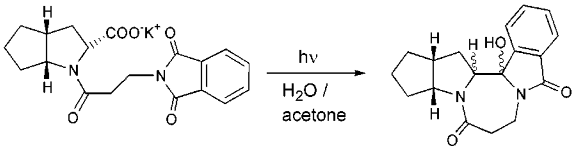
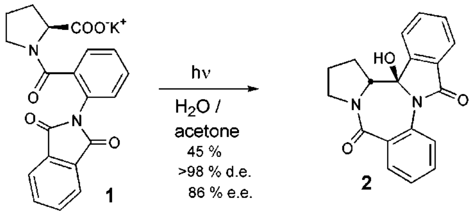
ABSTRACT



The decarboxylative photocyclization of potassium 2-azabicyclo[3.3.0]octanoate ethylene-linked to phthalimide leads to a mixture of two diastereoisomeric products. The overall noninduced diastereoselectivity is remarkably high, indicating a preference of spin–orbit coupling controlled 1,7-biradical combination process. Memory of chirality vanished due to free rotation about the connecting spacer bonds.

The concept of *memory of chirality*, as originally defined by Fuji and Kawabata,[1] operates for short-lived and/or conformationally restrained intermediates such as carbanions,[1] carbenium cations,[2] monoradicals,[3] and singlet biradicals.[4] Recently, we described the first example of high memory of chirality for a photochemical reaction which involves most probably a 1,7-triplet biradical.[5] As substrate, we used the proline-based acceptor−linker−donor couple **1** which, after electronic excitation and decarboxylation, cyclized to give the [1,4]pyrrolobenzodiazepine **2** with 86% ee (Scheme 1). This process serves as a new approach to these highly active DNA-alkylating reagents.[6] The stereogenic center in **1** is planarized after CO_2, extrusion but a remarkably high degree of chirality memory was retained.

Scheme 1



The simple diastereoselectivity of the radical combination process was very high (>98%), and only the *cis*-fused diastereoisomer was detected in the crude reaction mixture. With the stereolabeled substrate **3** derived from (*all-R*)-2-azabicyclooctanoate, the induced as well as the simple diastereoselectivity was remarkably high (Scheme 2). From the X-ray structures of products **2** and **4** and from the comparison of their respective CD-exciton chirality behavior,[7] it could be concluded that the photodecarboxylation/cyclization had occurred with *inversion* of configuration at the stereogenic α-center.

The 2-azabicyclo[3.3.0]octan-3-oic acid has been widely applied in the enantioselective synthesis of chiral targets[8] and in stereoselective catalytic reactions.[9] None of these

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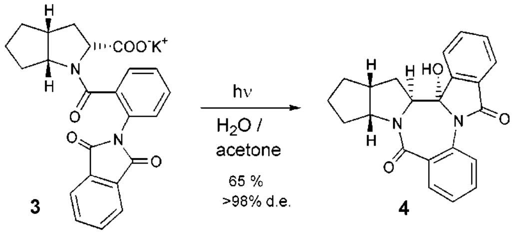
[1] Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373.
[2] Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689.
[3] Schmalz, H.-G.; de Koning, C. B.; Bernicke, D.; Siegel, S.; Pfletschinger, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1620.
[4] Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586.
[5] Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem., Int. Ed.* In press.
[6] Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.

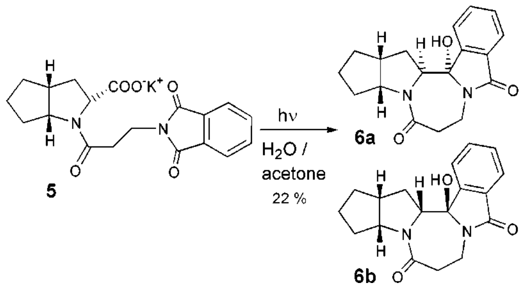
10.1021/ol006943i CCC: $20.00

Scheme 2



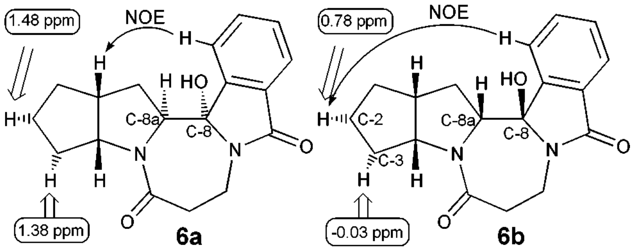
processes involved *direct* modification of the stereogenic center at C-3 coupled with decarboxylation. The absolute configuration *R* at C-3 can, however, easily be inverted into *S*.[10] From simple model inspections we expected the *endo* side of a 3-bicyclo[3.3.0]octyl radical to be strongly shielded due to its rooflike configuration.[11] Thus, the high induced diastereoselectivity in **4** could originate from a simple shielding effect. Furthermore, one might argue that the memory of chirality effect with **1** could also result from a bond formation process which proceeds more or less concerted with the extrusion of CO_2. In this case, the inversion phenomena as well as the pronounced simple diastereoselectivity accounts for a strong preorientation. To evaluate these arguments, we applied the ethylene-linked donor−acceptor couple **5** as a conformationally more flexible substrate.[12] The photodecarboxylation proceeded with moderate chemoselectivity (ca. 40% of simple decarboxylation), and two diastereoisomers, **6a** and **6b** (0.9:1 ratio), were isolated in 22% yield (Scheme 3).

Scheme 3



The relative configurations of the newly formed stereogenic centers were determined by NOESY spectroscopy (Scheme 4). The most significant chemical shifts were these of the *endo* hydrogens at C-2 and C-3 of the anellated cyclopentane ring: in **6a** they were uninfluenced by the chemical modification and appeared around 1.4 ppm, whereas in the diastereoisomeric structure **6b** both hydrogens appeared strongly upfield-shifted at 0.78 and −*0.03 ppm* due to the anisotropic effect of the benzoate ring. A complete set of NOE effects corroborated the *trans* arrangement between the hydroxy group at C-8 and the bicyclooctane ring skeleton as well as the *exo* and *endo* configuration. How do we interpret these results? First, due to the flexible ethylene chain connecting the electron-accepting phthalimide and the bicyclooctanoate, chirality memory completely vanished and the cyclization product with *retention* of configuration at C-8a slightly dominated. This clearly shows that the bond formation step is not concerted with CO_2 extrusion. Second, the noninduced diastereoselectivity of the biradical combination step remains high even for the unusual reaction from the *endo* side of the 3-bicyclo[3.3.0]octyl radical. A mechanistic model developed by us for the photocycloaddition of triplet excited carbonyls with cycloalkenes connects (noninduced) product diastereoselectivity with the spin−orbit coupling controlled geometry of the 1,4-biradical during the triplet−singlet crossing (ISC) process.[13] Likewise, the 1,7-triplet biradicals after extrusion of CO_2 approach a reactive conformation which allows rapid crossing in to the singlet potential energy surface. Spin inversion is directly coupled with bond formation, and thus the product configuration reflects the reactive configuration of the 1,7-triplet biradical.

Scheme 4



To learn more about the effect of ring size on the direction and degree of stereocontrol, we investigated a much simpler substrate with the stereolabel incorporated into the linker chain: the alanine-connected phthalimide−proline couple **7**. This substrate gave a diastereoisomeric mixture of *cis* and *trans* products (with respect to the newly formed stereogenic centers) **8a** and **8b** (Scheme 5). Thus, both stereoisomers were formed with high asymmetric induction with respect to the linear anellation of the pyrrolidine ring (*retention* of configuration) but with unusually low noninduced diastereoselectivity.[14] The situation changed again for the photochemical 1,5-cyclization:[15] the *o*-aminodiphenylmethane

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(7) Berova, N.; Borhan, B.; Dong, J. G.; Guo, J.; Huang, X.; Karnaukhova, E.; Kawamura, A.; Lou, J.; Matile, S.; Nakanishi, K.; Rickman, B.; Su, J.; Tan, Q.; Zanze, I. *Pure Appl. Chem.* **1998**, *70*, 377.

(8) For example: Wilken, J.; Kossenjans, M.; Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Liebigs Ann.* **1997**, 573.

(9) Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2353. Wilken, J.; Kossenjans, M.; Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4437. Wilken, J.; Gröger, H.; Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2761.

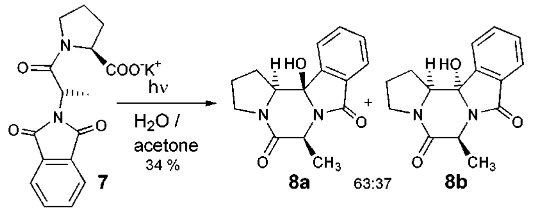
(10) Wilken, J.; Thorey, C.; Gröger, H.; Haase, D.; Saak, W.; Pohl, S.; Muzart, J.; Martens, J. *Liebigs Ann.* **1997**, 2133.

(11) The corresponding carbanion gives a 14:86 *endo*/*exo* ratio with benzaldehyde: Wilken, J.; Martens, J. *Liebigs Ann.* **1997**, 563.

(12) From DCC/DMAP/HOBT-coupling of the benzyl ester of 2-azabicyclo[3.3.0]cctan-3-oic acid with *β*-alanine and subsequent hydrogenolytic debenzylation (overall yield: 73%).

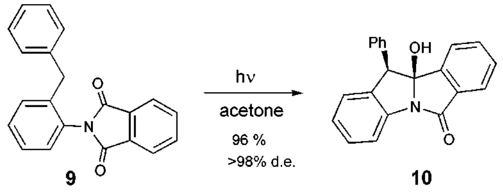
(13) Griesbeck, A. G.; Mauder, H.; Stadtmüller, S. *Acc. Chem. Res.* **1994**, *27*, 70. Griesbeck, A. G.; Buhr, S.; Fiege, M.; Lex, J.; Schmickler, H. *J. Org. Chem.* **1998**, *63*, 3847.

Scheme 5



derivative **9** gave (via H-abstraction) the *bis*-benzopyrrolizidine in high chemical yields exclusively as one diastereoisomer, **10** (Scheme 6).[16]

Scheme 6



These remarkable differences in noninduced radical−radical combination stereoselectivity are probably due to different reactive 1,*n*-triplet biradical geometries which represent crossing points from the triplet to the singlet energy surface. The assumption of pronounced stereoselectivity differences between singlet and triplet photocycloadditions was recently corroborated by a study of concentration effects.[17] The examples described herein involve highly diastereoselective 1,7-cyclization, nonselective 1,6-cyclization and again selective 1,5-cyclization. In all of these cases, the hydroxybenzyl radical is formed from the phthalimde part (Figure 1).

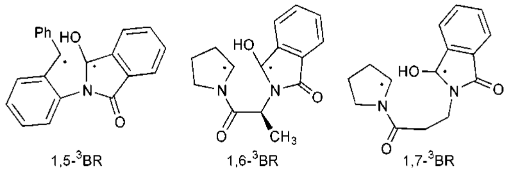


Figure 1.

The *cis* selectivity of the 1,5-biradical cyclization corresponds to the *endo* selectivity found in triplet Paternò−Büchi reactions.[18] An approach of the two radical centers as depicted in Figure 2 leads to conformer **A** which, after spin inversion, combines (the induced torque is indicated by the arrow) to give the product with the two small substituents (S = phenyl and hydroxy) at one side of the five-membered ring.

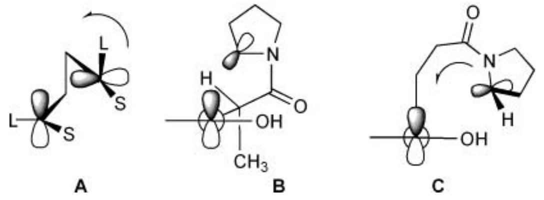


Figure 2.

The increase in chain length separating the radical centers increases the conformational flexibility and, for the intermediate situation **B**, reduces the simple diastereoselectivity. The triplet 1,7-biradical **C**, however, seems to regain stereochemical directivity due to the near-orthogonal alignment of the hydroxybenzyl plane and the linking group (*o*-phenylene or ethylene). Several X-ray analyses of substrates analogous to **1** or **3** proved this assumption for the solid-state structures.[19] Due to the increased conformational flexibility of the ethylene spacer in **5** (compared with the aryl spacer in **3**), the approach of the α-amino radical occurs from the *re* as well as the *si* side of the hydroxybenzyl radical center with comparable probability and the chirality memory effects vanishes.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is greatly acknowledged.

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[14] For stereoselective 1,6-photocyclization, see: Griesbeck, A. G.; Heckroth, H.; Schmickler, H. *Tetrahedron Lett.* **1999**, *40*, 3137.

[15] **Experimental Conditions. A: Photocyclization of 1, 3, 5, and 7.** A 15 mM solution of the potassium alkylcarboxylate in acetone/water (1:1 vol) was irradiated for 24 h at rt with coated low-pressure mercury lamps emitting at 300 nm. After treatment with a saturated aqueous $NaHCO_3$ solution and brine, extraction with AcOEt, and drying, the solvents were evaporated and the residue was purified by column chromatography. **B: Photocyclization of 9.** A 40 mM solution of **9** in acetone was irradiated for 48 h at rt, filtered over silica, and crystallized from acetone: 96% yield, mp 192−194 °C.

[16] X-ray structure of **10**: Lex, J.; Griesbeck, A. G.; Kramer, W. *Z. Kristallogr.* **2000**, *215*, 451.

[17] Griesbeck, A. G.; Fiege, M.; Bondock, S.; Gudipati, M. S. *Org. Lett.* **2000**, *2*, 3623.

[18] Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1990**, *112*, 1281. Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1991**, *113*, 6923.

[19] Griesbeck, A. G.; Kramer, W.; Oelgemöller, M.; Lex, J. Unpublished results.