Cycloaddition

Regioselective Inter- and Intramolecular Formal [4+2] Cycloaddition of Cyclobutanones with Indoles and Total Synthesis of (±)-Aspidospermidine**

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Hydrocarbazoles are found in the skeletons of many alkaloids, such as strychnine (1),^[1] kopsane (2),^[2] minfiensine (3),^[3] strictamine (4),^[4] and aspidospermidine (5; Scheme 1).



Scheme 1. Selected natural products with a hydrocarbazole skeleton.

Alkaloids and synthetic small molecules^[5] with a hydrocarbazole structure exhibit a broad range of important bioactivities.^[6] For the synthesis of structurally diverse and complex hydrocarbazoles, [4+2] cycloaddition to the C2-C3 positions of indoles has high synthetic potential, since two covalent bonds are formed in one step without the preintroduction of special substituents (e.g., a vinyl group^[3e,7]) on the indole. Such [4+2] cycloadditions of indoles are categorized into three types of Diels-Alder reaction (DAR): 1) normalelectron-demand DARs, in which strongly electron-deficient indoles that contain two electron-withdrawing groups at their 1- and 3-positions are used,^[8] 2) inverse-electron-demand DARs^[9] of highly electron-poor dienes, such as 1,2,4,5tetrazine,^[9b,c] and 3) DARs of photochemically induced radical cations with triarylpyrylium salts.^[10] In all of these DARs,^[11] the combination of indoles and enophiles $(4\pi$ donors) is restricted, and it is also difficult to change the regioselectivity of the cycloaddition. Therefore, the develop-

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ment of a general, efficient, and conceptually new strategy for the synthesis of structurally diverse hydrocarbazoles still remains important and challenging.

We describe herein the first example of a Lewis acid promoted formal [4+2] cycloaddition of cyclobutanones **6** with indoles (Scheme 2). This reaction enables the selective



Scheme 2. Formal [4+2] cycloaddition between indoles and 3-donor-substituted cyclobutanones **6**. PG = protecting group.

synthesis of both of the two possible regioisomeric hydrocarbazoles 8 and 9. Thus, we found that the zwitterionic intermediate 7, which was formed by the activation of 3donor-substituted cyclobutanones^[12] with a Lewis acid,^[13] reacted efficiently with indoles to give the corresponding hydrocarbazoles (8 or 9). A special activating group on the indole nucleus was not required, and a variety of indoles underwent the reaction, both in an intermolecular and in an intramolecular manner. The synthesis of a substructure of strictamine (4) and the total synthesis of (\pm)-aspidospermidine (5) by intramolecular cycloaddition reactions are also described herein.

The screening of Lewis acids for a formal [4+2] cycloaddition of indoles 10a-f with cyclobutanone 11a revealed that TiCl₄ was a suitable Lewis acid for indoles 10 a-d with an electron-withdrawing group (EWG) as the N-protecting group, whereas the use of EtAlCl₂ led to the formation of adducts 12e,f in good yields from the reactive indoles 10e,f (Scheme 3).^[14] Notably, the cycloaddition of indole **10e** without an N-protecting group proceeded smoothly to give 12e. We tested dichloromethane, toluene, and nitroethane as solvents and found that the use of nitroethane led to better yields of the cycloadducts derived from the N-arenesulfonylindoles 10 a,b and reactive indoles 10 e,f, whereas dichloromethane was suitable for the reaction of the N-alkoxycarbonylindoles 10 c,d.^[14] Good endo/exo selectivities were observed in the reactions of N-arenesulfonylindoles, whereas almost equal amounts of the endo and exo adducts were obtained in other cases. As described below, the removal of



Scheme 3. Lewis acid promoted formal [4+2] cycloaddition of indoles **10** with cyclobutanones **11** a-e to give hexahydro-2-oxocarbazoles **12** a-s. TiCl₄ was used as the Lewis acid and EtNO₂ as the solvent unless otherwise mentioned.^[14] The structures of the *endo* product, the yield of the isolated product, and the *endo/exo* ratio are given. [a] CH₂Cl₂ was used instead of EtNO₂. [b] EtAlCl₂ was used instead of TiCl₄. [c] Et₂AlCl was used as the Lewis acid. [d] For details about the configuration, see the Supporting Information. Ts = *p*-toluenesulfonyl, Ns = *o*-nitrobenzenesulfonyl, Cbz = benzyloxycarbonyl, Alloc = allyloxycarbonyl, Bn = benzyl.

the ethoxy group in cycloadducts **12** was straightforward. The stereostructure of *exo*-**12 c** as a representative *exo* adduct was determined unambiguously by X-ray crystallography, whereas that of an *endo* adduct was determined by NOE experiments.^[14]

Indoles bearing a methoxy, methyl, or bromo group at the 5-position reacted with 11a to give the corresponding cycloadducts 12g-i in good to high yields (Scheme 3). The propeller-like cycloadducts 12j,k were obtained from indoles fused with a five-membered ring. Structures similar to those of 12j and 12k are found in kopsane (2) and minfiensine (3), respectively. The mild Lewis acid Et₂AlCl was used for the synthesis of 12k, because the starting indole 10k and the product 12k were labile under strongly acidic conditions. Spirocyclobutanones 11b,c with a cyclopentane or cyclohexane ring reacted efficiently to afford spirocycloadducts 121,m. The bicyclic cyclobutanone 11e reacted with N-benzylindoles to give the tetracyclic products 12n (in 67% yield as a single diastereomer) and 120 (in 31% yield as a 67:33 mixture of diastereomers).^[15] This result suggests that the cyclobutanone ring of 11e was cleaved selectively to form the zwitterionic intermediate with the less substituted enolate.^[13a] Finally, cvclobutanone **11 d** with no alkyl substituents at the α position to the carbonyl group reacted with *N*-benzylindoles to afford compounds **12 q**–**s**.

Interestingly, reversed regioselectivity of the cycloaddition was observed when an indole had an electron-donating group (EDG) at the 3-position and an EWG on the nitrogen atom (Scheme 4). Thus, *N*-benzyloxycarbonyl 3-alkyl indoles reacted with cyclobutanone **11a** to afford hexahydro-3-



Scheme 4. Inverse regioselectivity in the formal [4+2] cycloaddition of 3-substituted indoles **13** with cyclobutanones **11 a–d** to give hexahydro-3-oxocarbazoles **14 a–g**. The structure of the *exo* product, the yield of the isolated product, and the *endo/exo* ratio are given.^[14] The *endo/exo* ratio was determined by ¹H NMR spectroscopy. [a] EtAlCl₂ was used instead of TiCl₄. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

oxocarbazoles **14 a,b** without formation of the regioisomeric hexahydro-2-oxocarbazoles **12**. 3-*tert*-Butyldimethylsilyloxyor 3-methylthio-substituted *N*-*p*-toluenesulfonylindoles also reacted with **11 a,d** to give hexahydro-3-oxocarbazoles **14 ce**.^[16] Two contiguous quaternary carbon centers were constructed efficiently in the formation of spiro compounds **14 f,g** through the cycloaddition of spirocyclobutanones **11 b,c**.

A diastereomeric mixture of 12c (*endo/exo* 54:46) was transformed smoothly into 15a by the Me₃SiOTf-promoted elimination of ethanol and isomerization (Scheme 5). The oxidation of 12c with DDQ, followed by treatment with Me₃SiOTf, gave enone 15b in 80% yield over the two steps. The conjugate addition of Me₂CuLi to enone 16a, which was prepared from 12p, proceeded stereoselectively to afford 16b. The methylthio group of *exo*-14e was removed with Raney nickel at a low temperature to give 17. Thus, we could synthesize both of the two possible regioisomers 12a and 17 selectively by our cycloaddition approach.

A proposed mechanism for the present cycloaddition is shown in Scheme 6. The zwitterion **18** generated from the cyclobutanone (in this case, **11 a**) reacts with an indole to form an iminium intermediate $19^{[17]}$ or a benzylic carbocation **21**, which then cyclizes to **20** (cyclization type A) or **22** (cyclization type B), respectively.^[18] When PG is an electron-donating group, such as a benzyl group, **19** is formed because the electron-donating group stabilizes the iminium cation. On the



Scheme 5. Transformation of adducts **12 c,p** and **14e**: a) Me₃SiOTf, CH₂Cl₂, 0°C, 1 h, then room temperature, 1 h, 86%; b) 1) DDQ, toluene, reflux, 45 min; 2) Me₃SiOTf, CH₂Cl₂, 0°C, 5 min, 80% (for two steps); c) 1) Me₃SiOTf, Et₃N, CH₂Cl₂, 0 \rightarrow 15 °C, 1.5 h; 2) Me₃SiOTf, CH₂Cl₂, 0°C \rightarrow RT, 1 h, 83% (for two steps); d) Me₂CuLi, BF₃·Et₂O, Et₂O/THF, $-78 \rightarrow$ 0°C, 3.5 h, 92%, single diastereomer; e) Raney nickel, EtOH/THF, -20°C, 1 h, 70%, d.r. 90:10. DDQ=2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Tf=trifluoromethanesulfonyl.



Scheme 6. Proposed mechanism for the formal [4+2] cycloaddition of 3-ethoxycyclobutanones with indoles.

other hand, the presence of an electron-withdrawing group on the nitrogen atom to disfavor 19 (compare 12p and 14a) and an electron-donating R group to favor 21 (compare 12c and 14a) promotes type B cyclization.

An intramolecular cyclization between a cyclobutanone and an indole was employed for the synthesis of a substructure 28 of (\pm) -strictamine (4; Scheme 7).^[19] Compound 26, the indole nitrogen atom of which was protected with an electronwithdrawing group (Ts), was used for the intramolecular formal [4+2] cycloaddition, since type-B cyclization was expected to give 28. A [2+2] cycloaddition between the TBS enol ether 23 and methyl chloro ketene was followed by reductive removal of the chloro group with a zinc-copper couple to give cyclobutanone 24. The reductive amination of 24 with tryptamine afforded 25, the secondary amino group and indole nitrogen atom of which were protected with an Alloc and a Ts group, respectively. Deprotection and oxidation of the hydroxy group gave the cycloaddition precursor 26. The key intramolecular [4+2] cycloaddition of 26 proceeded smoothly in the presence of the Lewis acid BF₃·Et₂O, and the desired product 28 was obtained in 87% yield. It was assumed that an intermediate 27 was formed by regioselective ring cleavage^[13a] of the α -methylcyclobutanone ring of 26 and that type-B intramolecular addition then gave 28.

We used a type-A intramolecular cyclization for the total synthesis of (\pm) -aspidospermidine (5;^[20] Scheme 8).^[21] The *N*-



Scheme 7. Synthesis of a substructure of 4: a) 2,2-dichloropropanoyl chloride, Zn, Et₂O, room temperature, 2 h; b) Zn/Cu, NH₄Cl, MeOH, room temperature, 1 h, 60% (for two steps), d.r. 66:34; c) tryptamine, NaBH(OAc)₃, CH₂Cl₂, room temperature, 14 h, quantitative; d) AllocCl, 10% aqueous Na₂CO₃, Et₂O, room temperature, 12 h, 87%; e) TsCl, NaOH, TBHSA, CH₂Cl₂, room temperature, 5 h, quantitative; f) TBAF, AcOH, THF, room temperature, 24 h; g) DMP, CH₂Cl₂, room temperature, 4 h, 80% (for two steps), d.r. 83:17; h) BF₃·Et₂O, CH₂Cl₂, room temperature, 2 h, 87%, d.r. 65:35. TBHSA = tetrabutylammonium hydrogen sulfate, TBAF = tetrabutylammonium fluoride, DMP = Dess-Martin periodinane.



Scheme 8. Total synthesis of (\pm) -**5**: a) CbzCl, CH₂Cl₂, room temperature, 15 h, 99%; b) Zn/Cu, Cl₃C(C=O)Cl, Et₂O, sonication, 0°C, 0.5 h, then room temperature, 14 h; c) Zn/Cu, NH₄Cl, MeOH, room temperature, 2 h, 85% (for two steps); d) ethylene glycol, TsOH/H₂O, benzene, reflux, 12 h, 95%; e) H₂, Pd/C, EtOH, room temperature, 3 h, quantitative; f) 3-indoleacetic acid, EDC, 0°C, 5 h, 89%; g) BnBr, NaH, DMF, room temperature, 2.5 h, 95%; h) 1 N HCl, EtOH, reflux, 3 h, 93%; i) Me₃SiOTf, toluene, reflux, 10 min, 46% (+ C22 epimer, 32%); j) N₂H₄·H₂O, Na, (CH₂OH)₂, 160–210°C, 18 h; k) LiAlH₄, THF, room temperature, 1 h, 71% (for two steps); l) H₂, Pd(OH)₂, EtOH, room temperature, 46 h, 93%. EDC=1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.

benzyl group of enamine **29**, which was readily prepared in five steps according to a procedure described by Norman and Heathcock,^[22] was exchanged for an *N*-Cbz group by treatment with benzyloxycarbonyl chloride.^[23] A [2+2] cycloaddition with dichloroketene, followed by reductive dechlorination, gave cyclobutanone **30** in 85 % yield over two steps. Protection of the carbonyl group of cyclobutanone **30** as an acetal and removal of the *N*-Cbz group afforded the piperidine derivative **31**. It was necessary to protect the carbonyl group of **30** because the 3-aminocyclobutanone that should be formed by removal of the *N*-Cbz group of **30** was too unstable to be isolated. Amine **31** was coupled with 3indoleacetic acid to give the corresponding amide, the indole nitrogen atom of which was protected with a benzyl group. Hydrolysis of the acetal group then gave the cycloaddition precursor **32**.^[24] After extensive screening of Lewis acids and optimization of the reaction conditions, the intramolecular [4+2] cycloaddition of **32** proceeded to give the desired pentacyclic compound **34** in 46% yield along with the C22 epimer of **34** (32%). The cyclobutanone ring of **32** was cleaved regioselectively as observed for the bicyclic cyclobutanone **11e**, and an intramolecular type-A cyclization of **33** gave **34**. Wolff–Kishner reduction^[20i,25] of **34**, followed by reduction of the amide group with LiAlH₄ and removal of the *N*-Bn group with Pd(OH)₂,^[20k] gave (±)-**5**. Notably, in this synthesis, the C and E rings of **5**, with an angular C22 ethyl substituent, were constructed in a single step.

In conclusion, we have developed a new formal [4+2] cycloaddition between indoles and cyclobutanones that can proceed in both an intra- and an intermolecular manner, and we have shown that cyclobutanones were excellent fourcarbon-atom donors for various indoles. The regioselectivity of the cycloaddition was controlled by the indole substituents, and it was demonstrated that the two possible regioisomers of a cycloaddition product could be synthesized selectively. The wide reaction scope and unique orientation control were applied to the synthesis of a tetracyclic substructure of (\pm) -strictamine (4) and the total synthesis of (\pm) -aspidospermidine (5). We believe that this regioselective method offers rapid and reliable access to structurally diverse hydrocarbazoles from abundant indoles.

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- For reviews, see: a) J. S. Cannon, L. E. Overman, Angew. Chem.
 2012, 124, 4362-4386; Angew. Chem. Int. Ed. 2012, 51, 4288-4311; b) M. Mori, Heterocycles 2010, 81, 259-292; c) J. Bonjoch, D. Solé, Chem. Rev. 2000, 100, 3455-3482.
- [2] a) M. Greshoff, *Ber. Dtsch. Chem. Ges.* 1890, 23, 3537–3550;
 b) H. Achenbach, K. Biemann, *J. Am. Chem. Soc.* 1965, 87, 4944–4950.
- [3] a) G. Massiot, P. Thépenier, M.-J. Jacquier, L. L. Men-Olivier, C. Delaude, *Heterocycles* 1989, 29, 1435–1438; b) A. B. Dounay, L. E. Overman, A. D. Wrobleski, J. Am. Chem. Soc. 2005, 127, 10186–10187; c) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, J. Am. Chem. Soc. 2008, 130, 5368–5377; d) L. Shen, M. Zhang, Y. Wu, Y. Qin, Angew. Chem. 2008, 120, 3674–3677; Angew. Chem. Int. Ed. 2008, 47, 3618–3621; e) S. B. Jones, B. Simmons, D. W. C. MacMillan, J. Am. Chem. Soc. 2009, 131, 13606–13607; f) G. Li, A. Padwa, Org. Lett. 2011, 13, 3767–3769; g) P. Liu, J. Wang, J. Zhang, F. G. Qiu, Org. Lett. 2011, 13, 6426–6428.
- [4] a) H. K. Schnoes, K. Biemann, J. Mokry, I. Kompis, A. Chatterjee, G. Ganguli, J. Org. Chem. **1966**, 31, 1641–1642; b) Y. Ahmad, K. Fatima, A. Rahman, J. L. Occolowitz, B. A. Solheim, J. Clardy, R. L. Garnick, P. W. Le Quesne, J. Am. Chem. Soc. **1977**, 99, 1943–1946; c) S. K. Bhattacharya, R. Bose, S. C. Dutta, A. B. Ray, S. R. Guha, Indian J. Exp. Biol. **1979**, 17, 598–600.
- [5] a) L. Kelman, *Neuropsychiatr. Dis. Treat.* 2008, 4, 49–54 (frovatriptan); b) J.-H. Ye, R. Ponnudurai, R. Schaefer, *CNS Drug Rev.* 2001, 7, 199–213 (ondansetron); c) T. Ishizuka, T.

Matsui, Y. Okamoto, A. Ohta, M. Shichijo, *Cardiovasc. Drug Rev.* **2004**, *22*, 71–90 (ramatroban).

- [6] A. Ramirez, S. Garcia-Rubio, Curr. Med. Chem. 2003, 10, 1891– 1915.
- [7] For recent studies, see: a) C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, Angew. Chem. 2008, 120, 9376–9379; Angew. Chem. Int. Ed. 2008, 47, 9236–9239; b) B. Tan, G. Hernández-Torres, C. F. Barbas, J. Am. Chem. Soc. 2011, 133, 12354–12357; c) Y.-J. Cao, H.-G. Cheng, L.-Q. Lu, J.-J. Zhang, Y. Cheng, J.-R. Chen, W.-J. Xiao, Adv. Synth. Catal. 2011, 353, 617–623.
- [8] a) E. Wenkert, P. D. R. Moeller, S. R. Piettre, J. Am. Chem. Soc. 1988, 110, 7188-7194; b) B. Biolatto, M. Kneeteman, P. Mancini, Tetrahedron Lett. 1999, 40, 3343-3346; c) I. Chataigner, E. Hess, L. Toupet, S. R. Piettre, Org. Lett. 2001, 3, 515-518; d) B. Biolatto, M. Kneeteman, E. Paredes, P. M. E. Mancini, J. Org. Chem. 2001, 66, 3906-3912; e) T. L. S. Kishbaugh, G. W. Gribble, Tetrahedron Lett. 2001, 42, 4783-4785; f) A. Chrétien, I. Chataigner, N. L'Hélias, S. R. Piettre, J. Org. Chem. 2003, 68, 7990-8002.
- [9] a) L. Lee, J. K. Snyder, Adv. Cycloaddit. 1999, 6, 119-171; b) M. Takahashi, H. Ishida, M. Kohmoto, Bull. Chem. Soc. Jpn. 1976, 49, 1725-1726; c) S. C. Benson, C. A. Palabrica, J. K. Snyder, J. Org. Chem. 1987, 52, 4610-4614; d) S. C. Benson, L. Lee, L. Yang, J. K. Snyder, Tetrahedron 2000, 56, 1165-1180; e) G. J. Bodwell, J. Li, Org. Lett. 2002, 4, 127-130; f) M. S. Raasch, J. Org. Chem. 1980, 45, 856-867; g) J.-E. Bäckvall, N. A. Plobeck, S. K. Juntunen, Tetrahedron Lett. 1989, 30, 2589-2592; h) M.-F. Hsieh, P. D. Rao, C.-C. Liao, Chem. Commun. 1999, 1441-1442.
- [10] a) A. Gieseler, E. Steckhan, O. Wiest, *Synlett* 1990, 275–277;
 b) A. Gieseler, E. Steckhan, O. Wiest, F. Knoch, *J. Org. Chem.* 1991, 56, 1405–1411; c) O. Wiest, E. Steckhan, *Tetrahedron Lett.* 1993, 34, 6391–6394; d) N. J. Saettel, O. Wiest, D. A. Singleton, M. P. Meyer, *J. Am. Chem. Soc.* 2002, *124*, 11552–11559.
- [11] For another approach, see: a) Q. Cai, S.-L. You, Org. Lett. 2012, 14, 3040–4043; b) R. L. Garnick, S. B. Levery, P. W. Le Quesne, J. Org. Chem. 1978, 43, 1226–1229.
- [12] For reviews, see: a) T. Seiser, T. Saget, D. N. Tran, N. Cramer, Angew. Chem. 2011, 123, 7884–7896; Angew. Chem. Int. Ed.
 2011, 50, 7740–7752; b) J. C. Namyslo, D. E. Kaufmann, Chem. Rev. 2003, 103, 1485–1537; c) E. Lee-Ruff, G. Mladenova, Chem. Rev. 2003, 103, 1449–1483; d) D. Belluš, B. Ernst, Angew. Chem. 1988, 100, 820–850; Angew. Chem. Int. Ed. Engl. 1988, 27, 797–827; e) J. M. Conia, M. J. Robson, Angew. Chem. 1975, 87, 505–516; Angew. Chem. Int. Ed. Engl. 1975, 14, 473–485.
- [13] a) J. Matsuo, S. Sasaki, H. Tanaka, H. Ishibashi, J. Am. Chem. Soc. 2008, 130, 11600-11601; b) J. Matsuo, S. Sasaki, T. Hoshikawa, H. Ishibashi, Org. Lett. 2009, 11, 3822-3825; c) J. Matsuo, S. Negishi, H. Ishibashi, Tetrahedron Lett. 2009, 50, 5831-5833; d) E. A. Allart, S. D. R. Christie, G. J. Pritchard, M. R. J. Elsegood, Chem. Commun. 2009, 7339-7341; e) A. T. Parsons, J. S. Johnson, J. Am. Chem. Soc. 2009, 131, 14202-14203; f) J. Matsuo, R. Okado, H. Ishibashi, Org. Lett. 2010, 12, 3266-3268; g) M. M. A. R. Moustafa, B. L. Pagenkopf, Org. Lett. 2010, 12, 4732-4735; h) G. Shan, P. Liu, Y. Rao, Org. Lett. 2011, 13, 1746-1749.
- [14] See the Supporting Information for details.
- [15] N-Benzylindoles bearing a 2-(triisopropylsilyloxy)ethyl group, a 2-bromoethyl group, or an ethoxycarbonylmethyl group at the 3-position did not react with **11e**.
- [16] An attempted cycloaddition of **11e** with 3-*tert*-butyldimethylsilyloxy-substituted *N*-*p*-toluenesulfonylindole did not proceed.
- [17] The stepwise mechanism was suggested by the formation of an open-chain by-product in the synthesis of **12 f** (Scheme 3).^[14]
- [18] Similar regioselectivity was reported previously: Z. Song, Y.-M. Zhao, H. Zhai, Org. Lett. 2011, 13, 6331–6333.
- [19] For synthetic studies, see: a) M.-L. Bennasar, E. Zulaica, M. López, J. Bosch, *Tetrahedron Lett.* **1988**, *29*, 2361–2364; b) M.-L.

Angew. Chem. Int. Ed. 2013, 52, 906–910

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Bennasar, E. Zulaica, A. Ramírez, J. Bosch, *J. Org. Chem.* **1996**, *61*, 1239–1251; c) R. V. Edwankar, C. R. Edwankar, O. A. Namjoshi, J. R. Deschamps, J. M. Cook, *J. Nat. Prod.* **2012**, *75*, 181–188.

[20] For selected studies towards the synthesis of 5, see: a) G. Stork, J. E. Dolfini, J. Am. Chem. Soc. 1963, 85, 2872-2873; b) J. Harley-Mason, M. Kaplan, J. Chem. Soc. Chem. Commun. 1967, 915-916; c) G. Büchi, K. E. Matsumoto, H. Nishimura, J. Am. Chem. Soc. 1971, 93, 3299-3301; d) J.-Y. Laronze, J. Laronze-Fontaine, J. Lévy, J. Le Men, Tetrahedron Lett. 1974, 15, 491-494; e) T. Gallagher, P. Magnus, J. Huffman, J. Am. Chem. Soc. 1982, 104, 1140-1141; f) L. E. Overman, M. Sworin, R. M. Burk, J. Org. Chem. 1983, 48, 2685-2690; g) P. Le Ménez, N. Kunesch, S. Liu, E. Wenkert, J. Org. Chem. 1991, 56, 2915-2918; h) M. A. Toczko, C. H. Heathcock, J. Org. Chem. 2000, 65, 2642-2645; i) J. P. Marino, M. B. Rubio, G. Cao, A. De Dios, J. Am. Chem.

Soc. **2002**, *124*, 13398–13399; j) F. De Simone, J. Gertsch, J. Waser, *Angew. Chem.* **2010**, *122*, 5903–5906; *Angew. Chem. Int. Ed.* **2010**, *49*, 5767–5770; k) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188.

- [21] R. Delgado, S. B. Blakey, Eur. J. Org. Chem. 2009, 1506-1510.
- [22] M. H. Norman, C. H. Heathcock, J. Org. Chem. 1988, 53, 3370– 3371.
- [23] The Cbz-protected enamine was prepared in three steps from δvarelolactam; see Ref. [20j].
- [24] For the synthesis of 32, there is little possibility of a successful [2+2] cycloaddition of an enamide containing an indole skeleton, since the reactivity of an enamide is very low as compared with that of an enecarbamate; see also: A. R. de Faria, C. R. R. Matos, C. R. D. Correia, *Tetrahedron Lett.* 1993, 34, 27–30.
- [25] E. Wenkert, K. Orito, D. P. Simmons, N. Kunesch, J. Ardisson, J. Poisson, *Tetrahedron* 1983, 39, 3719–3724.