Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 3265

Asymmetric organocatalytic synthesis of 4,6-bis-(1*H*-indole-3-yl)-piperidine-2 carboxylates†

Sabilla Zhong,[a,b] Martin Nieger,[c] Angela Bihlmeier,[d] Min Shi*[a] and Stefan Bräse*[b,e]

Received 30th January 2014,
Accepted 21st March 2014

DOI: 10.1039/c4ob00234b

www.rsc.org/obc

We developed an asymmetric organocatalytic synthesis of 4,6-bis(1*H*-indole-3-yl)-piperidine-2-carboxylates using 10 mol% of a chiral phosphoric acid. The products, which are novel bisindole-piperidine-amino acid hybrids, can be obtained in one step from 3-vinyl indoles with imino esters in dichloromethane at room temperature after 1 h of reaction time. A variety of these compounds could be synthesized in up to 70% yield and 99% ee, and they were experimentally and computationally analyzed regarding their relative and absolute stereochemistry.

Introduction

Bisindole alkaloids can be widely found in nature, exhibiting various interesting biological activities which can be medicinally important. There are numerous compounds of marine origin bearing two isolated indoles on one heterocycle (Fig. 1), such as nortopsentins (**1a–d**)[1,2] and their analogs which exhibit antitumor,[2d,3–8] antiproliferative, antiplasmodial,[9] and antifungal[3] activities. The dragmacidins[10] (*e.g.* **2a–b**) possess antitumor,[11,12] phosphatase inhibitory,[13] and antiviral[14] activities and their derivatives hamacanthins[15] (*e.g.* **3**) have antitumor,[16] antifungal,[17] and antibacterial[16,18] properties.

In the late 80s, 3-vinylindole (**4a**) was found to be a versatile building block for the synthesis of heterocycles fused to an indole moiety. This is due to the fact that 3-vinylindole acts as a diene in the Diels–Alder reaction with various electron-deficient olefins and aza dienophiles, *e.g.* nitrosobenzene, DEAD, diethyl mesoxalate, benzoquinones, and maleimides.[19–22] The reactivity of 3-vinylindoles can be utilized in the synthesis of carbazoles.[19,20,23,24] Also reactions with singlet oxygen are reported.[25] In the last few years, the first asymmetric organocatalytic Diels–Alder reactions of 3-vinylindoles were reported, including thiourea-catalyzed reactions with maleimides or quinones[26] and indolones.[27] Furthermore, the reactivity of 3-vinylindole can be that of a dienophile, furnishing Povarov-type products when reacted with electron-rich arylimines.[28] In that work, it was proven that the intermediate could be trapped by an excess of 3-vinylindole (5 equiv.) leading to an interesting and complex bisindole consisting of two units of vinylindole and one unit of arylimine. However, the work of Ricci *et al.* mainly focused on the asymmetric Povarov reaction and they made no further investigations

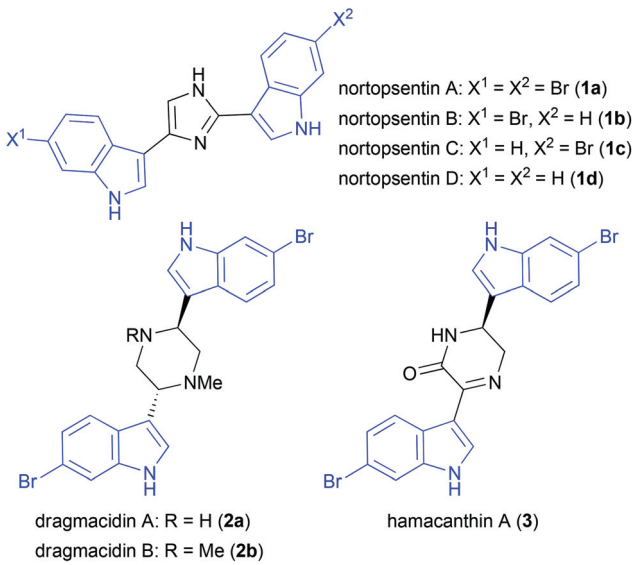


Fig. 1 Structures of some indole alkaloids containing two isolated indole moieties.

[a]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: mshi@mail.sioc.ac.cn; Fax: +86 21 6416 6128*
[b]*Karlsruhe Institute of Technology (KIT), Institute of Organic Chemistry, Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany. E-mail: braese@kit.edu; Tel: +49 721 608-48581*
[c]*Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, P.O. Box 55, 00014 University of Helsinki, Finland*
[d]*Karlsruhe Institute of Technology (KIT), Institute of Physical Chemistry and Center for Functional Nanostructures (CFN), Fritz-Haber-Weg 2, D-76131 Karlsruhe, Germany*
[e]*Institute of Toxicology and Genetics, Hermann-von-Helmholtz-Platz 1, D-76344 Eggenstein-Leopoldshafen, Germany*

†Electronic supplementary information (ESI) available: Experimental details, analytic data (including NMR spectra, HPLC traces), details of CD spectral calculations, and crystallographic data for **9aa**. CCDC 977608. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00234b

towards the synthesis and the relative/absolute configuration of the resulting bisindole-piperidine-hybrid.

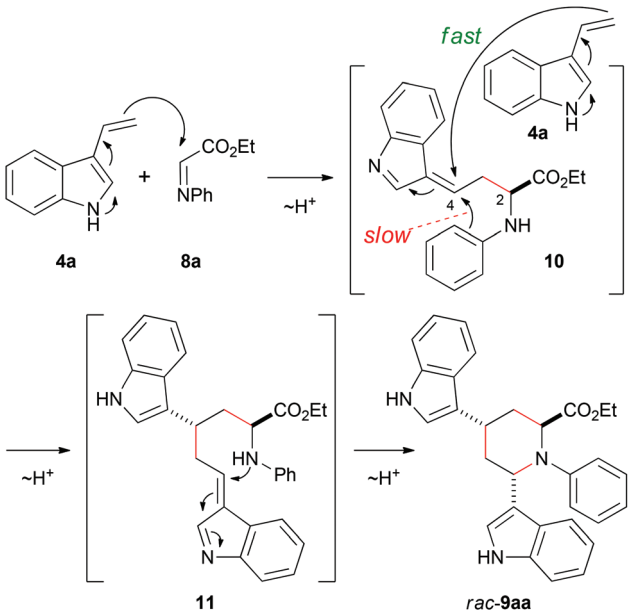
Results and discussion

Reaction between 3-vinylindole (4a) and glyoxylate imine (8a)

We took on the interesting and dual reactivity of 3-vinylindoles and explored their behaviour towards various types of imines in order to create nitrogen heterocycles bearing new stereocenters. Imines **5–8a** were prepared according to established procedures[29–32] and treated with 3-vinylindole (**4a**)[33] in toluene (Scheme 1). Only in the case of ethyl glyoxylate-derived imine **8a** a reaction was observed. It turned out that 3-vinylindole did not act as a diene in this reaction, but the formed product arised from a multicomponent addition of two equivalents of 3-vinylindole (**4a**) and one equivalent of imino ester **8a**. Interestingly, this reaction occurred at room temperature with a short reaction time (3.5 h) without any addition of the catalyst. The product is similar to that reported by Ricci *et al.* but has an ethyl ester moiety at the 2-position (therefore being an amino acid derivative) instead of a phenyl substituent and does not require a large excess of vinylindole.

A plausible mechanism for this reaction is given in Scheme 2. After the first addition, the second molecule 3-vinylindole (**4a**) is able to attack the stabilized intermediate **10**. This step proceeds considerably faster than the nucleophilic attack of the aromatic phenyl ring at position 4, since only traces of the corresponding Povarov reaction product were found. An intramolecular ring closure of **11** finally gives piperidine-2-carboxylic ester *rac*-**9aa** as the only possible regioisomer.

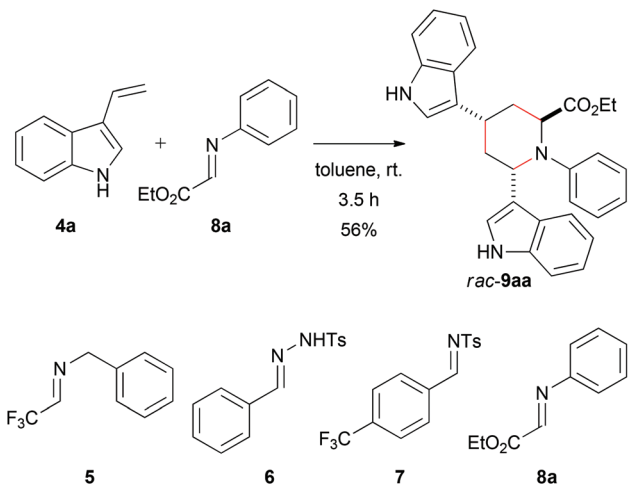
For the reaction, a free NH group is necessary on the indole moiety, as in a reaction of N-methylated derivative (1-methyl-3-vinyl-1*H*-indole) with glyoxalate imine **8a**, no product could be isolated. This supports the proposed mechanism for the racemic formation of **9aa** in Scheme 2, which involves several proton transfers of the indole NH. Furthermore, following attempts to protect the indole-NH functionalities in the reaction product **9aa** with trifluoroacetate or tosylate failed.



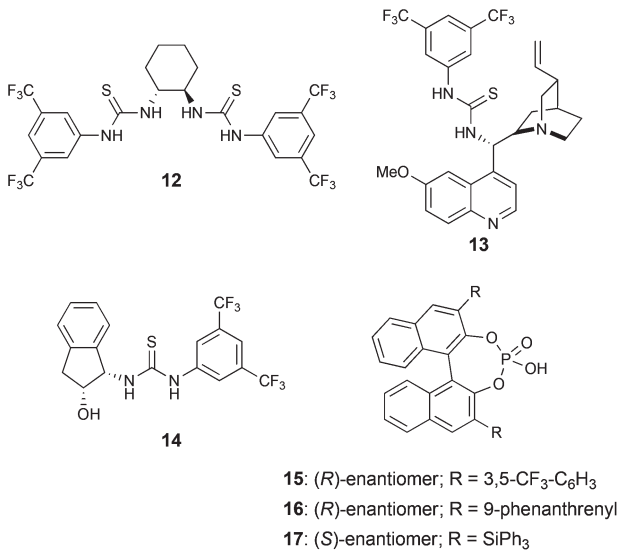
Scheme 2 Proposed mechanism for the formation of bisindole *rac*-**9aa**.

Asymmetric synthesis of bisindole 9aa and optimization

Next, the asymmetric reaction of **4a** and **8a** was investigated. It was envisioned that chiral thiourea catalysts, such as **12–14** (Fig. 2), would be able to interact strongly with imine **8a** *via* H-bond catalysis.[26,27,34–37] However, the results employing these catalysts were not satisfying, giving almost no enantioinduction with 7.5% ee at most and often strongly diminished



Scheme 1 Racemic synthesis of bisindole *rac*-**9aa** with imino ester **8a** (see ESI† for more information) and attempted reactions with other imines **5–7**.



15: (*R*)-enantiomer; R = 3,5-CF_3-C_6H_3
16: (*R*)-enantiomer; R = 9-phenanthrenyl
17: (*S*)-enantiomer; R = $SiPh_3$

Fig. 2 Screened thiourea and phosphoric acid catalysts.

Table 1 Screening of thiourea catalysts (upper part), phosphoric acid catalysts (middle part), and solvents (lower part)

Entry	Cat. [mol%]	Solvent	Time	Temp.	Yield[a]	ee[b]
1[c]	**12** [20]	*n*-Hexane–toluene 2 : 1	4 h	rt.	22%	3%
2	**12** [20]	CH_2Cl_2	2 h	−78 °C	13%	3%
3[c]	**13** [20]	*n*-Hexane–toluene 2 : 1	18 h	rt.	15%	0%
4	**14** [20]	CH_2Cl_2	16 h	rt.	52%	2%
5	**14** [20]	*n*-Hexane	16 h	rt.	13%	7.5%
6	**15** [10]	Toluene	2 h	rt.	46%	69%
7	**15** [10]	Toluene	2.5 h	0 °C	51%	56%
8[d]	**15** [10]	Toluene	5 h	0 °C	54%	54%
9	**16** [10]	Toluene	2 h	rt.	47%	88%
10	**16** [10]	Toluene	5 h	−78 °C	Traces	—
11	**16** [10]	Toluene	4 h	−40 °C	30%	79%
12[c]	**16** [10]	Toluene	1 h	rt.	60%	92%
13[c]	**16** [10]	Toluene	20 min	50 °C	69%	91%
14[c]	**17** [10]	Toluene	1 h	rt.	43%	72%
15[c]	**16** [10]	THF	4.5 h	rt.	70%	91%
16[c]	**16** [10]	Et_2O	1.17 h	rt.	65%	93%
17[c]	**16** [10]	CH_2Cl_2	1 h	rt.	64%	94%
18[c]	**16** [10]	MeCN	1.5 h	rt.	67%	87%
19[e]	**16** [10]	CH_2Cl_2	1 h	rt.	57%	94%
20[f]	**16** [10]	CH_2Cl_2	1 h	rt.	61%	98%

Unless stated otherwise, the catalyst and 3-vinylindole (**4a**, 0.1 mmol) were added to a solution of imine **8a** (0.05 mmol) in an absolute solvent (1 mL). After consumption of the starting material the crude mixture was purified *via* preparative TLC or column chromatography (PE–EtOAc 3 : 1). [a] Isolated yield. [b] Determined by HPLC. [c] Reaction was carried out with 0.1 mmol of **4a** and 0.1 mmol of **8a**. [d] Imine **8a** was prepared *in situ* from ethyl glyoxylate and aniline. [e] Reaction was performed on a gram scale (14 mmol of **4a** and 7 mmol of **8a**). [f] Reaction was carried out with 0.3 mmol of **4a** and 0.1 mmol of **8a**.

yields (Table 1) compared to those without employing any catalyst. The enantioselectivity could not be improved when the temperature was lowered (entry 2). A considerable improvement of the yield was observed when utilizing catalyst **14** in CH_2Cl_2; however, in this case the product was nearly racemic (entry 4).

Chiral phosphoric acids[38] represent another catalyst class widely used in organic chemistry, especially in the strongly related asymmetric (vinylogous) Mannich-type reactions and also employed by Ricci *et al.* in the aforementioned paper.[28] Three phosphoric acid catalysts **15–17** (Fig. 2), which are commercially available, and different reaction conditions were screened towards their ability to promote an asymmetric reaction of 3-vinylindole (**4a**) and imine **8a** to yield the substituted piperidine **9aa**.

The following conclusions can be drawn considering the results in Table 1: (i) all of the screened chiral phosphoric acid catalysts give good enantiomeric excesses; (ii) good yields could be obtained while only using 1 equivalent of each reactant; (iii) in some cases, employing a catalyst leads to a considerable improvement of the chemical yield to 60% or more (entries 12 and 13) compared to the reaction without any catalyst; (iv) the best catalyst in terms of yield and ee (>90%) is catalyst **16** (entries 12 and 13). At 50 °C, the reaction is complete after only 20 min with a yield close to 70% and an ee of 91% (entry 13); (v) lowering the temperature did not improve the results, it even gave diminished yields and ees (entries 10 and 11); (vi) preparing imine **8a** *in situ* from ethyl glyoxylate and aniline gives product **9aa**, too, but with no significant change of yield and ee (entry 8), nevertheless this shows that even a four component reaction to form **9aa** is feasible. Also, in the catalyzed reaction, the formation of Povarov products was completely suppressed.

Having found an efficient catalyst **16**, several solvents were screened in order to improve the enantiomeric excess. The yields in any solvent remained quite stable (57–70%, entries 15–20). The enantiomeric excess was optimized in dichloromethane (up to 98%, entry 20). Acetonitrile caused the ee value to drop (entry 18).

Relative and absolute configuration of 9aa

The relative configuration was identified through NOE correlations (Fig. 3). In the proposed conformer structure, both indole-3-yl groups are standing in the equatorial position, thus minimizing steric interactions between one another, and the ethyl ester is standing axially, possibly to avoid the interaction with the *N*-phenyl group. In addition, crystals of **9aa** could be obtained by recrystallization from iPrOH. The absolute configuration was unequivocally proven by X-ray crystallography using the effects of anomalous dispersion (Fig. 3). Thus a (2*S*,4*S*,6*S*) configuration could be confirmed (see also ESI† and CCDC 977608).

As our sample of **9aa** had an enantiomeric purity of ee = 94%, it is generally possible that the single crystal used for the X-ray diffraction study consisted of the minor enantiomer. To exclude this eventuality, we measured the electronic circular dichroism (CD) spectrum, which is a property of the bulk compound, in methanol at 20 °C. Furthermore, using the TURBOMOLE program package,[39] the spectrum was calculated with time-dependent density functional theory methods[40] (along with the C-4 epimer of **9aa**, which was clearly ruled out as a possible product, see also ESI†). Because of good agreement of the calculated spectrum of **9aa** with the experimental spectrum, we can ensure the proposed (2*S*,4*S*,6*S*) configuration (Fig. 4).

Scope of the reaction

As the reaction conditions were optimized, the scope of the reaction was explored by using differently substituted 3-vinyl-

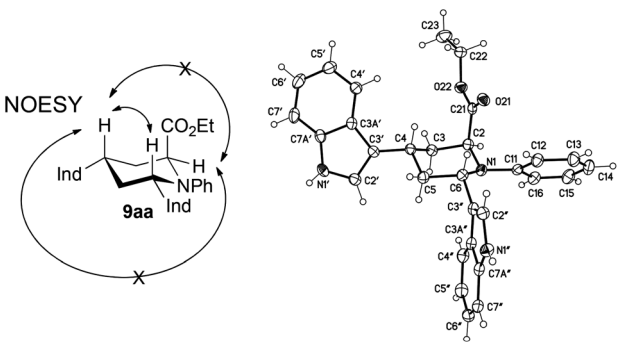


Fig. 3 Structure of bisindole **9aa**, left: experimentally determined NOE correlations; right: molecular structure of **9aa** (displacement parameters are drawn at 50% probability level, CCDC 977608).

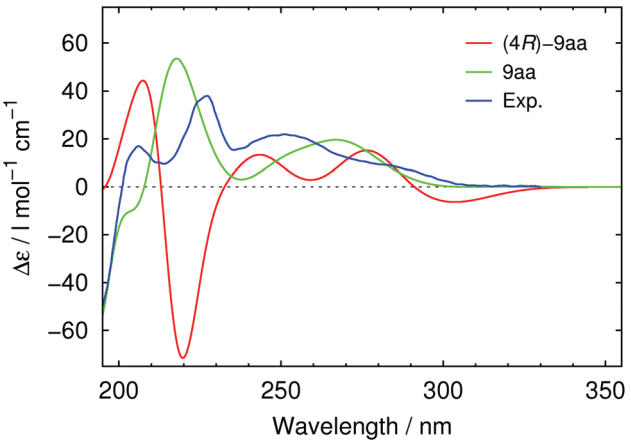
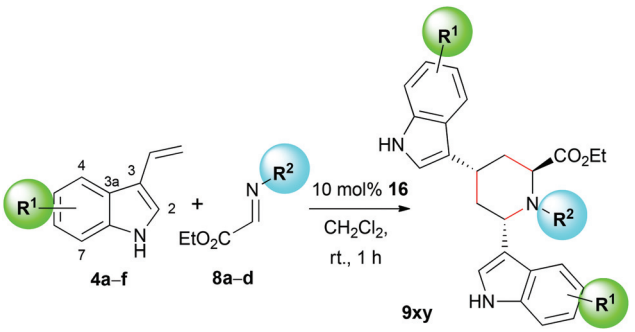


Fig. 4 Experimental CD spectrum (blue curve, 94% ee) and calculated CD spectra of **9aa** (green curve) and its C-4 epimer (red curve); conditions: c = 0.05 mg mL^{-1}, MeOH, 20 °C.

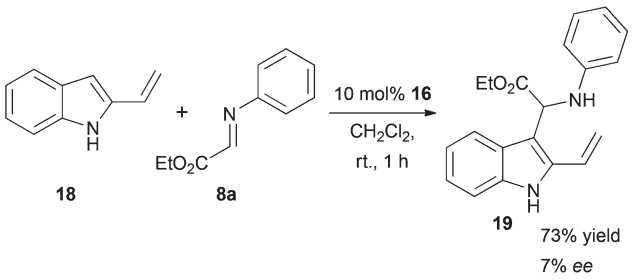
indoles **4a–f** and glyoxalate imines **8a–d**. The reactions were carried out on a 0.1 mmol scale with catalyst **16** in dichloromethane. In all cases, high ees were achieved, while depending on the substitution pattern and varying stability of the different vinylindoles the yields were sometimes considerably lower than for the unsubstituted substrate **4a** (Table 2). We believe that in the case of vinylindoles **4d** and **4e** (entries 7 and 8), the low yields are due to the fast decomposition of the

Table 2 Synthesis of bisindole derivatives **9*xy***



Entry	Equiv. (**4*x*** : **8*y***)	R^1 (**4*x***)	R^2 (**8*y***)	Yield^a of **9*xy***	ee^b
1	1 : 1	H (**4a**)	Ph (**8a**)	64% **9aa**	94%
2	1 : 1	5-Br (**4b**)	Ph (**8a**)	51% **9ba**	90%
3	2 : 1	7-Me (**4c**)	Ph (**8a**)	43% **9ca**	>99%
4	2 : 1	5-Br (**4b**)	3,5-Me$_2$-C$_6$H$_3$ (**8b**)	58% **9bb**	94%
5	2 : 1	H (**4a**)	4-OMe-C$_6$H$_4$ (**8c**)	56% **9ac**	97%
6	2 : 1	H (**4a**)	4-Br-C$_6$H$_4$ (**8d**)	28% **9ad**	93%
7	2 : 1	5-OMe (**4d**)	Ph (**8a**)	21% **9da**	87%
8	2 : 1	5-Br-7-Me (**4e**)	Ph (**8a**)	25% **9ea**	75%
9	2 : 1	6-F (**4f**)	Ph (**8a**)	34% **9fa**	89%
10	2 : 1	6-F (**4f**)	4-OMe-C$_6$H$_4$ (**8c**)	48% **9fc**	n.d.

Catalyst **16** (10 mol%) and 3-vinylindole derivative **4** were added to a solution of imine **8** in CH_2Cl_2 (1–2 mL). After stirring for 1 h at rt., the crude mixture was purified *via* preparative TLC. [a] Isolated yield after column chromatography or preparative TLC. [b] Determined by HPLC; n.d. = not determined (no separation of enantiomers achieved).



Scheme 3 Synthesis of amino acid derivative **19**.

starting material. Derivatives **4d** and **4e** must be used immediately after preparation and even when stored in the freezer at −20 °C, they decompose within a few days. Furthermore, we discovered that the reaction proceeded diastereoselectively, leading to one main product. Apart from the shown isomers, we observed, in most cases, traces of one or two other diastereomers which could not completely be separated from the main product. In the ^{1}H NMR spectra, their signals can be seen and distinguished especially in the range of 4.5–5.5 ppm adjacent to the main product signals (see ESI†).

We also found that this kind of reactivity in a three-component reaction is only possible with 3-vinylindoles and not the isomeric 2-vinylindole (**18**), which certainly supports the necessity of a free electron pair on the nitrogen in conjugation to the vinyl group. Under the same reaction conditions with catalyst **16**, we observed the typical reactivity of unsubstituted indoles with electrophiles, which is that of a spontaneous Friedel–Crafts addition,[41,42] giving amino acid derivative **19** with only poor enantioselectivity (Scheme 3).

Having proven the generality of the reaction by applying the conditions on various substrates, we explored whether an upscaling of the reaction was possible. Upscaling (2 g scale) the reaction of bisindole **9aa** still gave a comparable yield of 57% with an unchanged ee of 94%. Furthermore, we exemplarily showed that catalyst **16** was recyclable (see ESI† for more information).

Conclusions

In conclusion, we developed a powerful three-component, enantioselective, and organocatalytic synthesis of 4,6-bis(1*H*-indole-3-yl)piperidine 2-carboxylates **9*xy*** utilizing easily accessible 3-vinylindoles and imino esters and a chiral phosphoric acid. The reaction proceeds fast (1 h) and diastereoselectively at room temperature, building three new bonds and three new stereogenic centers in one step, and furnishes the products in yields up to 70% and ees up to 99%. The reaction can be conducted on a gram scale and the catalyst is recyclable; furthermore, it is also possible to run it as a four-component reaction. The products are highly functionalized, as they are bisindole-piperidine-amino acid hybrids, and they resemble medicinally interesting natural products. Their activity towards various test organisms is currently under investigation.

Acknowledgements

We thank Dr. Jochen Bürck for CD spectral measurements, De Wang for helpful discussions, and Angela Wandler for experimental assistance. Financial support was realized by the Deutsche Telekom Stiftung, the Karlsruhe House of Young Scientists (KHYS) (fellowships to S. Zhong), the Deutsche Forschungsgemeinschaft (CFN, project C3.3), and the Sino-German collaboration program GZ417.

Notes and references

1 H. H. Sun, S. Sakemi, S. Gunasekera, Y. Kashman, M. Lui, N. Burres and P. McCarthy, *U.S.*, US 4970226 A 19901113, 1990.
2 Syntheses and synthetic studies: (*a*) I. Kaswasaki, M. Yamashita and S. Ohta, *J. Chem. Soc., Chem. Commun.*, 1994, 2085; (*b*) I. Kawaski, M. Yamashita and S. Ohta, *Chem. Pharm. Bull.*, 1996, **44**, 1831; (*c*) X.-H. Gu, X.-Z. Wan and B. Jiang, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 569; (*d*) C. J. Moody and J. R. A. Roffey, *ARKIVOC*, 2000, **1**, 393; (*e*) B. Jiang and X.-H. Gu, *Bioorg. Med. Chem.*, 2000, **8**, 363; (*f*) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2000, **2**, 2121; (*g*) P. M. Fresneda, P. Molina and M. A. Sanz, *Synlett*, 2001, 218.
3 S. Sakemi and H. H. Sun, *J. Org. Chem.*, 1991, **56**, 4304.
4 I. Mancini, G. Guella, C. Debitus, J. Waikedre and F. Pietra, *Helv. Chim. Acta*, 1996, **79**, 2075.
5 X.-H. Gu, X.-Z. Wan and B. Jiang, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 569.
6 (*a*) P. Diana, A. Carbone, P. Barraja, A. Montalbano, A. Martorana, G. Dattolo, O. Gia, L. Dalla Via and G. Cirrincione, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2342; (*b*) P. Diana, A. Carbone, P. Barraja, G. Kelter, H.-H. Fiebig and G. Cirrincione, *Bioorg. Med. Chem.*, 2010, **18**, 4524.
7 A. Carbone, B. Parrino, P. Barraja, V. Spanò, G. Cirrincione, P. Diana, A. Maier, G. Kelter and H.-H. Fiebig, *Mar. Drugs*, 2013, **11**, 643.
8 A. Carbone, M. Pennati, B. Parrino, A. Lopergolo, P. Barraja, A. Montalbano, V. Spanò, S. Sbarra, V. Doldi, M. De Cesare, G. Cirrincione, P. Diana and N. Zaffaroni, *J. Med. Chem.*, 2013, **56**, 7060.
9 S. Alvarado, B. F. Roberts, A. E. Wright and D. Chakrabarti, *Antimicrob. Agents Chemother.*, 2013, **57**, 2362.
10 Syntheses and synthetic studies: (*a*) B. Jiang, J. M. Smallheer, C. Amaral-Ly and M. A. Wuonola, *J. Org. Chem.*, 1994, **59**, 6823; (*b*) C. R. Whitlock and M. P. Cava, *Tetrahedron Lett.*, 1994, **35**, 371; (*c*) T. Kawasaki, H. Enoki, K. Matsumura, M. Ohyama, M. Inagawa and M. Sakamoto, *Org. Lett.*, 2000, **2**, 3027; (*d*) B. Jiang and X.-H. Gu, *Heterocycles*, 2000, **53**, 1559; (*e*) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2000, **2**, 3185; (*f*) N. K. Garg, R. Sarpong and B. M. Stoltz, *J. Am. Chem. Soc.*, 2002, **124**, 13179; (*g*) T. Kawasaki, K. Ohno, H. Enoki, Y. Umemoto and M. Sakamoto, *Tetrahedron Lett.*, 2002, **43**, 4245; (*h*) C.-G. Yang, G. Liu and B. Jiang, *J. Org. Chem.*, 2002, **67**, 9392; (*i*) C.-G. Yang, J. Wang and B. Jiang, *Tetrahedron Lett.*, 2002, **43**, 1063; (*j*) C.-G. Yang, J. Wang, X.-X. Tang and B. Jiang, *Tetrahedron: Asymmetry*, 2002, **13**, 383; (*k*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 9552; (*l*) N. K. Garg and B. M. Stoltz, *Tetrahedron Lett.*, 2005, **46**, 2423; (*m*) K. S. Feldman and P. Ngernmeesri, *Org. Lett.*, 2005, **7**, 5449; (*n*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5970; (*o*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *Synlett*, 2006, 3081; (*p*) F. Tonsiengsom, F. Y. Miyake, K. Yakushijin and D. A. Horne, *Synthesis*, 2006, 49; (*q*) M. Anstiss and A. Nelson, *Org. Biomol. Chem.*, 2006, **4**, 4135; (*r*) N. K. Garg and B. M. Stoltz, *Chem. Commun.*, 2006, 3769; (*s*) R. J. Huntley and R. L. Funk, *Org. Lett.*, 2006, **8**, 4775; (*t*) M. Ikoma, M. Oikawa and M. Sasaki, *Tetrahedron Lett.*, 2008, **49**, 7197; (*u*) M. Seto, J. L. Roizen and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2008, **47**, 6873; (*v*) K. S. Feldman and P. Ngernmeesri, *Org. Lett.*, 2011, **13**, 5704; (*w*) D. Mandal, A. D. Yamaguchi, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2011, **133**, 19660; (*x*) K. S. Feldman and P. Ngernmeesri, *Synlett*, 2012, 1882.
11 S. Kohmoto, Y. Kashman, O. J. McConnell, K. L. Rinehart Jr., A. Wright and F. Koehn, *J. Org. Chem.*, 1988, **53**, 3116.
12 A. E. Wright, S. A. Pomponi, S. S. Cross and P. McCarthy, *J. Org. Chem.*, 1992, **57**, 4772.
13 R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler and A. R. Carroll, *J. Nat. Prod.*, 1998, **61**, 660.
14 A. Cutignano, G. Bifulco, I. Bruno, A. Casapullo, L. Gomez-Paloma and R. Riccio, *Tetrahedron*, 2000, **56**, 3743.
15 Syntheses and synthetic studies: (*a*) T. Kawasaki, T. Kouko, H. Totsuka and K. Hiramatsu, *Tetrahedron Lett.*, 2003, **44**, 8849; (*b*) T. Kouko, K. Matsumura and T. Kawasaki, *Tetrahedron*, 2005, **61**, 2309.
16 B. Bao, Q. Sun, X. Yao, J. Hong, C. Lee, Y. H. Cho and J. H. Jung, *J. Nat. Prod.*, 2007, **70**, 2.
17 S. P. Gunasekera, P. J. McCarthy and M. Kelly-Borges, *J. Nat. Prod.*, 1994, **57**, 1437.
18 K.-B. Oh, W. Mar, S. Kim, J.-Y. Kim, T.-H. Lee, J.-G. Kim, D. Shin, C. J. Sim and J. Shin, *Biol. Pharm. Bull.*, 2006, **29**, 570.
19 E. M. Beccalli, A. Marchesini and T. Pilati, *Tetrahedron*, 1996, **52**, 3029.
20 (*a*) U. Pindur and L. Pfeuffer, *Chimia*, 1986, **40**, 124; (*b*) U. Pindur and L. Pfeuffer, *Monatsh. Chem.*, 1986, **110**, 95; (*c*) U. Pindur, *Heterocycles*, 1988, **27**, 1253; (*d*) U. Pindur and L. Pfeuffer, *Monatsh. Chem.*, 1989, **120**, 27; (*e*) U. Pindur and M. H. Kim, *Chem. Ztg.*, 1991, **115**, 237.
21 B. Saroja and P. C. Srinivasan, *Synthesis*, 1986, 748.
22 J. D. Lambert and Q. N. Porter, *Aust. J. Chem.*, 1981, **34**, 1483.
23 W. E. Noland and S. R. Wand, *J. Org. Chem.*, 1979, **44**, 4402.
24 H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino and S. Hibino, *Tetrahedron*, 2000, **56**, 5807.

25 X. Zhang, S. I. Khan and C. S. Foote, *J. Org. Chem.*, 1993, **58**, 7839.
26 (*a*) C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2008, **47**, 9236; (*b*) C. Gioia, L. Bernardi and A. Ricci, *Synthesis*, 2010, 161.
27 B. Tan, G. Hernández-Torres and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 12354.
28 G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi and A. Ricci, *Chem. Commun.*, 2010, **46**, 327.
29 Imine **8a** was synthesized similar to: E. Borrione, M. Prato, G. Scorrano, M. Stivanello and V. Lucchini, *J. Heterocycl. Chem.*, 1988, **25**, 1831.
30 Synthesis of **5**: Q.-Y. Zhao, Z.-L. Yuan and M. Shi, *Adv. Synth. Catal.*, 2011, **353**, 637.
31 Synthesis of **6**: V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2003, **125**, 10926.
32 Synthesis of **7**: Z. Li, X. Ren, Y. Shi and P. Ouyang, *Synth. Commun.*, 2007, **37**, 713.
33 Synthesis of **4a**: this compound was synthesized with a slightly modified procedure according to ref. 26*a*, see also ESI.†
34 (*a*) Y. Sohtome, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2004, **45**, 5589; (*b*) N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976; (*c*) Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu and Y.-C. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 2456; (*d*) C. Rampalakos and W. D. Wulff, *Adv. Synth. Catal.*, 2008, **350**, 1785; (*e*) Y. Sohtome, N. Takemura, R. Takagi, Y. Hashimoto and K. Nagasawa, *Tetrahedron*, 2008, **64**, 9423; (*f*) X. Li, H. Deng, S. Luo and J.-P. Cheng, *Eur. J. Org. Chem.*, 2008, 4350; (*g*) D. Enders, K. Gottfried and G. Raabe, *Adv. Synth. Catal.*, 2010, **352**, 3147.
35 (*a*) J. Song, Y. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 6048; (*b*) J. Song, H.-W. Shih and L. Deng, *Org. Lett.*, 2007, **9**, 603; (*c*) L. Cheng, L. Liu, H. Jia, D. Wang and Y.-J. Chen, *J. Org. Chem.*, 2009, **74**, 4650; (*d*) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding and Y. Wu, *Synlett*, 2005, 603; (*e*) B. Vakulya, S. Varga, A. Csampai and T. Soos, *Org. Lett.*, 2005, **7**, 1967.
36 R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576.
37 Some original work on thiourea catalysis: (*a*) M. S. Sigman, P. Vachal and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 1279; (*b*) P. R. Schreiner and A. Wittkopp, *Org. Lett.*, 2002, **4**, 217.
38 Reviews: (*a*) M. Terada, *Chem. Commun.*, 2008, 4097; (*b*) M. Terada, *Synthesis*, 2010, 1929; (*c*) S. J. Connon, *Angew. Chem., Int. Ed.*, 2006, **45**, 3909; (*d*) D. Kampen, C. M. Reisinger and B. List, *Top. Curr. Chem.*, 2010, **291**, 395.
39 TURBOMOLE, Version 6.4; University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, Turbomole GmbH since 2007; http://www.turbomole.com.
40 (*a*) F. Furche, R. Ahlrichs, C. Wachsmann, E. Weber, A. Sobanski, F. Vögtle and S. Grimme, *J. Am. Chem. Soc.*, 2000, **122**, 1717; (*b*) S. Grimme, F. Furche and R. Ahlrichs, *Chem. Phys. Lett.*, 2002, **361**, 321–328.
41 B. Jiang and Z.-G. Huang, *Synthesis*, 2005, 2198.
42 Y.-Q. Wang, J. Song, R. Hong, H. Li and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 8156.

