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Stereoselective Synthesis of (+)-Aspidofractinine

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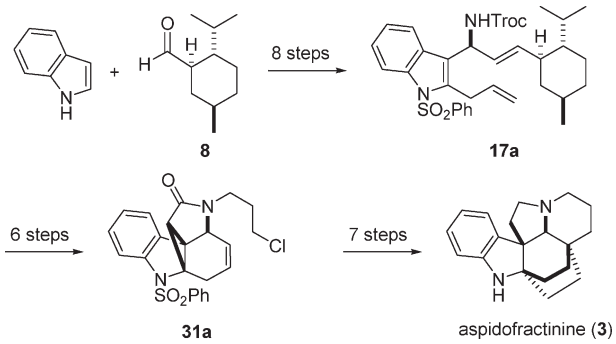

We describe the synthesis of (+)-aspidofractinine, the enantiomer of a naturally occurring alkaloid of the kopsane family. Key features of the synthesis include a stereospecific cyanate to isocyanate rearrangement on a chiral scaffold, a ring-closing alkene metathesis to cleave the chiral auxiliary, and a chemoselective cyclopropanation to introduce the quaternary carbon at position 7 of aspidofractinine.

Introduction

Aspidofractinine is a complex alkaloid[1] isolated from the leaves of *Pleiocarpa tubicana* and *Aspidosperma refractum*, and its structure was elucidated in 1963 by Schmid and coworkers (Figure 1).[2] It has since been isolated from *Aspidosperma pyrifolium*[3] and other *Apocynaceae* species.[4] Aspidofractinine is considered the parent compound of a large family of related indole alkaloids often isolated from the genus *Kopsia* that are widely found throughout Southeast Asia (Figure 1). Many members of this family were found to reverse multidrug resistance in vincristine-resistant KB cells.[5]

The synthesis of aspidofractinine was first completed by Ban and his collaborators in 1976, who obtained aspidofractinine as a racemic mixture.[6] Since then, it has been synthesized four times as a racemic mixture, including a second synthesis from the Ban group.[7] The kopsane alkaloids have an unusually strained carbon skeleton with three all-carbon quaternary centers, two of which are contiguous.

Retron **6** is central in our strategy, and it contains all the carbon atoms needed to construct rings A−E of aspidofractinine (Scheme 1). We planned to access retron **6** rapidly and stereoselectively from our chiral auxiliary *p*-menthane-3-carboxaldehyde **8** and use to advantage the fact that the latter could be cleaved via a ring-closing metathesis reaction all the while producing ring E of the target molecule. Cyclopropane **5** turned out to be a crucial intermediate in solving a nagging problem of aromatization. As in the syntheses of Ban and

(1) Hesse, M. *The Alkaloids, Nature's Curse or Blessing?* Wiley-VCH: Zürich, 2002; 413 pp. (b) Fattorusso, E., Taglilatela-Scafati, O., Eds. *Modern Alkaloids*; Wiley-VCH: Weinheim, Germany, 2008; 665 pp. (c) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 2−197.

(2) (a) Djerassi, C.; Budzikiewicz, H.; Owellen, R. J.; Wilson, J. M.; Kump, W. G.; Le Count, D. J.; Battersby, A. R.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 742–751. (b) Guggiesberg, A.; Gorman, A.; Bycroft, B. W.; Schmid, H. *Helv. Chim. Acta* **1969**, *52*, 76–89. (c) Patel, M. B.; Schumann, D.; Bycroft, B. W.; Schmid, A. *Helv. Chim. Acta* **1964**, *47*, 1147–1153.

(3) Xavier de Araujo, J. J.; Antheaume, C.; Trindade, R. C. P.; Schmitt, M.; Bourguignon, J. J.; Goulart, S. A. E. *Phytochem. Rev.* **2007**, *6*, 183–188.

(4) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302–1307.

(5) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2008**, *71*, 53–57.

(6) Ban, Y.; Homna, Y.; Oishi, T. *Tetrahedron Lett.* **1976**, *14*, 1111–1114.

(7) (a) Ban, Y.; Ohnuma, T.; Oishi, T.; Kinoshita, H. *Chem. Lett.* **1986**, 927–930. (b) Cartier, D.; Ouahrani, M.; Lévy, J. T. *Tetrahedron Lett.* **1989**, *30*, 1951–1954. (c) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. *Tetrahedron Lett.* **1989**, *30*, 3429–3432. (d) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677–7682.

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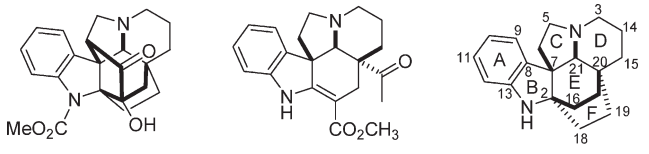
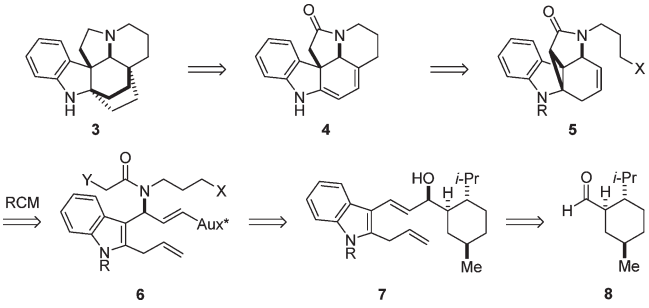


FIGURE 1. Three alkaloids from the kopsane family.

SCHEME 1. Retrosynthesis of (+)-Aspidofractinine



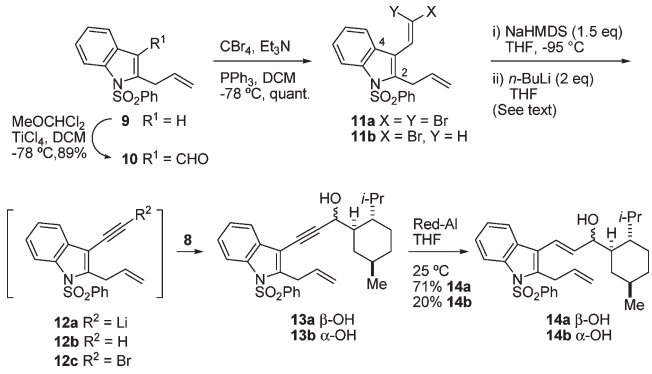
Wenkert and their co-workers, we elected to use a Diels–Alder cycloaddition on intermediate **4** to introduce the C18–C19 bridge and complete the synthesis.[6,7d]

Results and Discussion

To prepare one of the key intermediates in the synthesis, namely, compound **7**, we needed to stereoselectively add the appropriate vinylmetal to aldehyde **8**. The addition of $AlMe_3$, in catalytic amount or in excess, to a mixture of a vinyllithium and a chiral aldehyde leads to a significant increase in the expected Felkin–Ahn selectivity.[8] We use this methodology, whenever possible, to add vinyllithiums to *p*-menthane-3-carboxaldehyde **8** and typically get ratios of diastereomeric alcohols such as **7** in the range of 50–100:1. However, preparing the requisite vinylbromide **11b** (Scheme 2) from aldehyde **10**[9] proved impractical under a variety of conditions, and its conversion to a vinyllithium was problematic, giving several unidentified products after addition of aldehyde **8**. We speculated that the problem stemmed from deprotonation elsewhere in the molecule, particularly at the allylic position. In such a case, the addition of the corresponding alkynyllithium can be a suitable alternative, giving ratios in the range of 5–10:1.

We thus set out to prepare alkyne **12b**. The direct Seyferth–Gilbert alkynylation method[10] from **10** did not work, and adding 2 equiv of *n*-BuLi to **11a** (made from **10** using the Corey–Fuchs procedure) resulted in a multitude of products, many of which had a propen-1-yl unit at the 2-position of the indole moiety. It appears that the strong base can deprotonate the allyl fragment, which allows the migration

SCHEME 2



of its double bond. Fortunately, a one-pot sequence, involving the elimination of HBr with NaHMDS at −95 °C to yield **12c**, the generation of the alkynyllithium with *n*-BuLi, and the addition of *p*-menthane-3-carboxaldehyde **8** to this mixture, gave propargyl alcohol **13a**. The two diastereomers thus formed were more easily separable after reduction of the triple bond with Red-Al, which gave a 71% yield of pure allylic alcohol **14a** after two steps, along with 20% of its pure diastereomer **14b**.

Transposing the chirality of the carbinol in **14a** was achieved using a cyanate-to-isocyanate rearrangement.[11] The most frequently used method to generate the cyanate is to dehydrate the corresponding carbamic acid, which in this case is compound **15a** (Scheme 3). Here, reaction time, temperature, and acidity of the milieu were crucial to avoid decomposition as alcohol **14a**, carbamate **15a**, and isocyanate **16a** are all prone to decomposition. Fortunately, an excellent yield for the sequence **14a** → **15a** → **16a** was obtained after careful optimization (Scheme 3). The diastereomeric ratio indicated for **16a** was determined from the Troc derivative **17a** obtained by treatment with Cl_3CCH_2OH and $Ti(O\text{-}i\text{-}Pr)_4$.[12] We later found that it was possible to add 2,2,2-trichloroethanol directly to the reaction flask after dehydration of carbamate **15a**, and without the need to add a Lewis acid, to obtain a good yield of **17a** in a single step.

Having successfully introduced the C–N bond with control of its absolute stereochemistry, the chiral auxiliary could now be cleaved, concomitantly forming ring E of aspidofractinine. Ring-closing metathesis (RCM) using 5 mol % of Grubbs' second generation catalyst provided compound **18** in 92% (Scheme 4).[13] Byproduct **19** is volatile and can be easily removed from the crude reaction mixture under reduced pressure. It can be recovered and converted back to auxiliary **8** in good yield by ozonolysis.[13]

(8) Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* **2002**, *4*, 4735–4737.

(9) 2-Allylindole 9 was prepared according to (a) Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331–2332. (b) Saulnier, M. G.; Gribble, W. J. *Org. Chem.* **1982**, *47*, 757–761. Its acylation to give **10** was carried out using the protocol of (c) Bennasar, M.-L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett.* **2004**, *45*, 6283–6285.

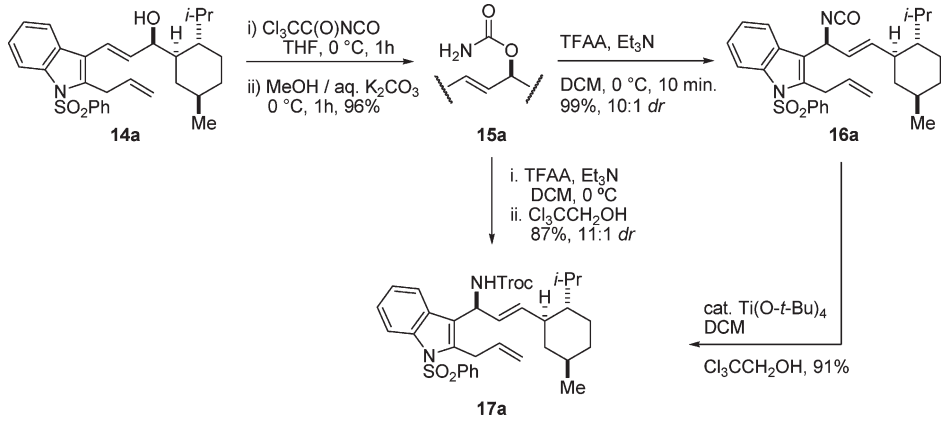
(10) Seyferth, D.; Marmor, R. S.; Gilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(11) For a recent account, see (a) Ichikawa, Y. *Synlett* **2007**, 2927–2936. (b) Roy, S.; Spino, C. *Org. Lett.* **2006**, *8*, 939. (c) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 939–943. (d) Ichikawa, Y.; Ito, T.; Isobe, M. *Chem.—Eur. J.* **2005**, *11*, 1949–1957. (e) Matsukawa, Y.; Isobe, M.; Kotsuki, H.; Ichikawa, Y. *J. Org. Chem.* **2005**, *70*, 5339–5341. (f) Nishiyama, T.; Isobe, M.; Ichikawa, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4372–4375.

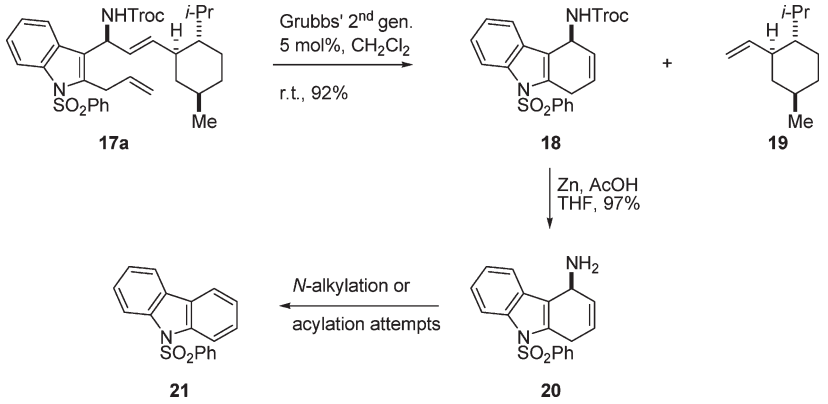
(12) Spino, C.; Joly, M.-A.; Godbout, C.; Arbour, M. *J. Org. Chem.* **2005**, *70*, 6118–6121.

(13) (a) Spino, C.; Boisvert, L.; Douville, J.; Roy, S.; Lauzon, S.; Minville, J.; Gagnon, D.; Chabot, C. *J. Organomet. Chem.* **2006**, *691*, 5336–5355. (b) Boisvert, L.; Beaumier, F.; Spino, C. *Can. J. Chem.* **2006**, *84*, 1290–1293.(c) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; Vols. 1–3.

SCHEME 3



SCHEME 4



Carbamate **18** and many homologous compounds aromatize rather easily to give the known carbazole **21**.[14] This fact dictated our strategy for the ensuing sequence of reactions. Indeed, removal of the Troc protecting group gave a high yield of amine **20**, which simply could not be derivatized under pain of aromatization to carbazole **21**. Mancini as well as Magnus and their respective co-workers have also experienced a similar challenge, and the latter resorted to concealing one double bond in the structure until later in their sequence when the system could no longer aromatize.[15] We instead elected to carry out the RCM cleavage after installing the required carbon chains on the nitrogen, temporarily postponing the aromatization problem.

In the event, the amine **22** was produced in quantitative yield from **17a**, and it was first alkylated and then acylated to give **23a** or **23b** without difficulty (Scheme 5). RCM on either compound proceeded uneventfully, at room temperature, to give the central intermediates **24a** or **24b**. Note that RCM could not be performed later in the sequence because any attempt to make the C6−C7 bond on an open structure like **23a** or **23b** (cf. Scheme 5) would most likely lead to the product with the wrong stereochemistry at C-7 or at best to mixtures of stereoisomers.

Our initial design called for a biscyclization to convert **24** to **26**, as shown in Scheme 6. Rather appealing, direct, and, in principle, feasible, this strategy was nevertheless short-lived, and we quickly realized that the C6−C7 bond could not be prepared in this way. Aromatization was again the culprit, and any attempt to effect the first cyclization (**24a** → **25**) failed, giving mostly carbazole **21** or its desulfonylated analogue. Magnus,[16] Rodriguez,[17a] Banwell,[17b] Heathcock,[17c] Rawal,[17d] and their respective research teams were able to effect such an electrophilic cyclization on substrates that could not aromatize. Like them, we varied the leaving group in **24** (X = Cl, Br, OMs, OH), added silver triflate to promote its departure, and tried removing the sulfone group under reducing or basic conditions to augment the nucleophilicity of the indole, all to no avail.

Thinking that the aromatization problem could be curtailed if a less potent leaving group replaced the amide, we tried the same cyclization on tertiary amine **27**. However, aromatization to give carbazole **21** took place just as easily, and in hindsight, it is probable that the formation of the aziridinium **28** is fast, thus creating an even better leaving group than the amide. The aziridinium functionality might

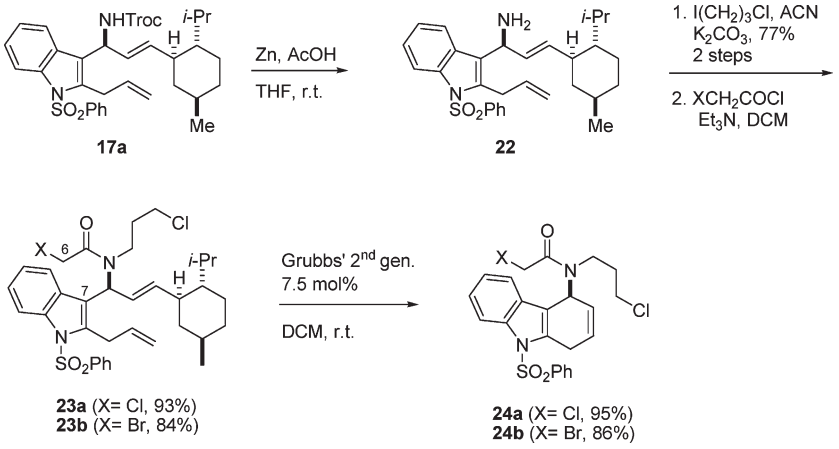
(14) (a) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603–7610. (b) Bennasar, M.-L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett.* **2004**, *45*, 6283–6285.

(15) (a) Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **1999**, *40*, 3343–3346. (b) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105–2114.

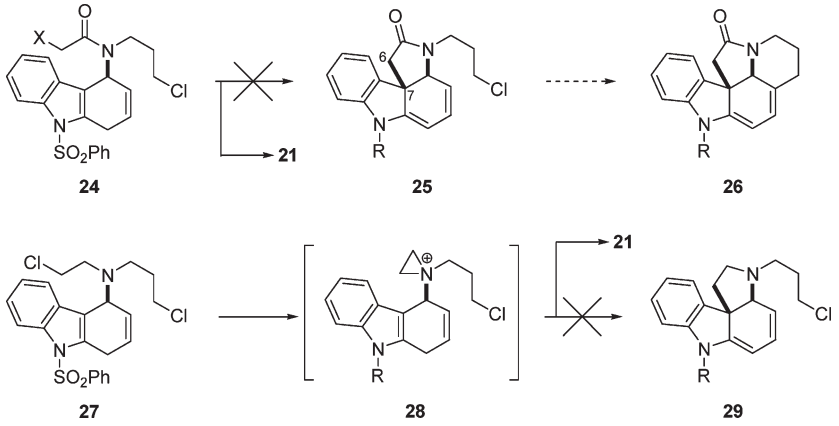
(16) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750–4757.

(17) (a) Rodriguez, J. G.; Urrutia, A. *Tetrahedron* **1999**, *55*, 11095–11108. (b) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213–215. (c) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642–2645. (d) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

SCHEME 5



SCHEME 6



have been an excellent electrophile for the desired cyclization had it been faster than aromatization.

We also attempted a radical cyclization from **24a**, thinking that we could initiate the reaction at the haloketone in the presence of a primary chloride. While this assumption was correct, only reduced product (**24c**, X = H) was obtained. This unfortunate result is nonetheless in line with results published by the Magnus group, who obtained decomposition products when attempting to close the C6−C7 bond via a radical pathway.[16]

We solved our problem by carrying out a chemoselective cyclopropanation of the indole C5−C6 double bond. Indolic alkenes have been cyclopropanated before,[18] but we are aware of only one report[19] of an intermolecular chemoselective cyclopropanation in a similar system involving a dibromocarbene. However, in that case, neither the yield nor the ratio of products obtained was given. We prepared α-diazoketone **30** in one step from α-bromoketone **24b** (Scheme 7).[20] To our delight, the Cu(I)-catalyzed cyclopropanation of **30** occurred with complete chemoselectivity to give a 76% isolated yield of **31a**.[21] A single-crystal X-ray diffraction analysis revealed both the relative and absolute stereochemistry of **31a** (see Supporting Information for the crystal structure and ORTEP diagram). Pleased, we went about the business of closing ring D. The radical cyclization of the iodide **31b** gave 92% yield of **32**. It is worth noting that the rigid structure of **31b** is likely responsible for this high-yielding radical cyclization. Indeed, 6-exotrig cyclizations to make decalines are known to be poor-yielding,[22] and those to make decahydroquinolines appear to be worse.[23] In the latter case, hydrogen abstraction near the nitrogen competes. In the case of compound **31b**, the conformational rigidity may simultaneously hamper hydrogen abstraction and assist radical cyclization. Several atom transfer radical cyclization protocols were also investigated, all of which proceeded without success.[22]

Reductive deprotection of the indole nitrogen in **32** with the sodium anthracene radical anion concomitantly removed the N-protecting group and ring-opened the cyclopropane to

(18) (a) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L. *J. Org. Chem.* **1977**, *42*, 3945–6949. (b) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544–547. (c) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277–4280. (d) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063–8069. (e) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835–6838.

(19) (a) Ashmore, J. W.; Radlick, P. C.; Helmkamp, G. K. *Synth. Commun.* **1976**, *6*, 399–400. See also: (b) Dhanak, D.; Kuroda, R.; Reese, C. B. *Tetrahedron Lett.* **1987**, *28*, 1827–1829.

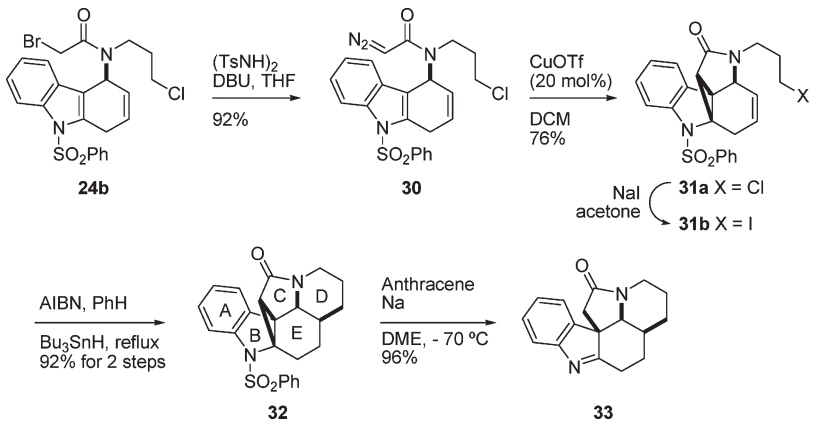
(20) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195–3197.

(21) (a) Gnad, F.; Poleschak, P.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277–4280. (b) Welstead, W. J. Jr.; Stauffer, H. F. Jr.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544–547. (c) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945–3949. (d) Li, C.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 197–210.

(22) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, 2003; p 224.

(23) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSève, H.; Spino, C *J. Org. Chem.* **2008**, *73*, 6239–6250.

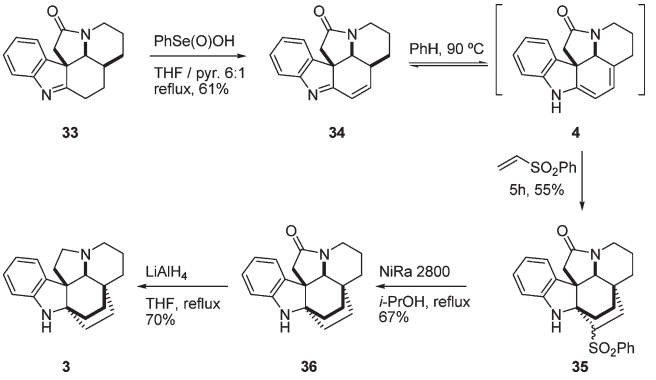
SCHEME 7



give imine **33** in 96% yield. These particular conditions are necessary as, with many other reducing conditions (e.g., sodium amalgam), **33** suffers an additional and unwanted reduction of the imine.

The synthesis of aspidofractinine was completed by oxidation of **33** with phenylseleninic acid to the known intermediate **34**, which had been prepared in a racemic form by Wenkert and his group (Scheme 8).[7d] We transformed **33** into aspidofractinine **3** using their protocol as shown in Scheme 8. When heated in benzene, enimine **34** is in equilibrium with its tautomer dienamine **4**, which is able to react with phenylvinylsulfone to give the Diels–Alder adduct **35**. The rest of the synthesis proceeded uneventfully to produce (+)-aspidofractinine **3**. All spectral data were identical with

SCHEME 8



those reported in the literature,[3,7b,24] except for the $[\alpha]_D$. We measured a value of +12 ($c = 0.27$, $CHCl_3$), which is close in value but of opposite sign to that reported in the literature [−14 ($c = 0.28$, $CHCl_3$)].[2c] There can be no doubt as to the absolute stereochemistry of our synthetic material,[25] and it is the same as the one assumed by Schmid and co-workers for natural **3** in 1964.[2c,26]

In conclusion, we have prepared for the first time optically active (+)-aspidofractinine **3** with the absolute configuration shown in Scheme 8. The synthesis proceeded in 21 steps from cheaply available indole. The overall yield is 2.1% with an average yield of 83% per step (Scheme 9). Notable are the highly stereoselective cyanate-to-isocyanate rearrangement, the mild RCM cleavage of the chiral auxiliary, the chemoselective cyclopropanation of **30**, and the high-yielding 6-exotrig radical cyclization of **31b**.

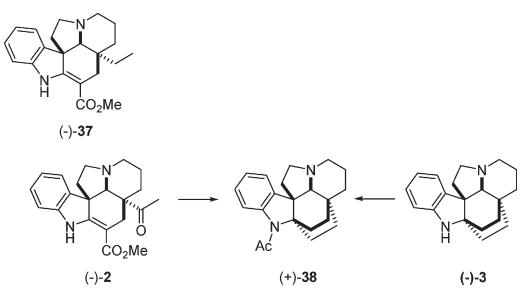
Experimental Section

(+)-Aspidofractinine (3). A suspension containing $LiAlH_4$ (14 mg, 0.369 mmol) and **36** (6.0 mg, 0.020 mmol) in 2.5 mL of tetrahydrofuran was stirred for 2 h at reflux. The reaction mixture was cooled to 0 °C, then 2.0 mL of diethyl ether, 14 μL of an aqueous solution of NaOH 15%, and 42 μL of water were added. After 15 min of agitation at 0 °C, the mixture was warmed to rt, and anhydrous magnesium sulfate was added. After 15 min of agitation, the mixture was filtered and rinsed with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography on a silica gel column with acetone and methanol (9:1) as eluant to give product **3** as a white amorphous

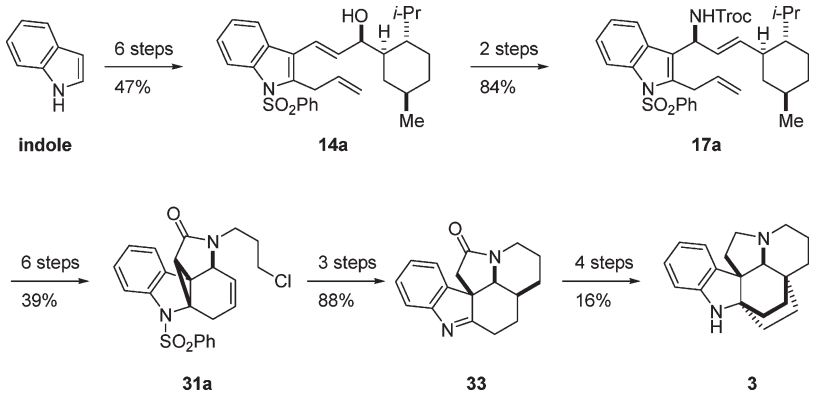
(24) We wish to thank Prof. J. Lévy and Dr. D. Royer for a copy of the ^{1}H NMR spectrum of racemic **3** for comparison. See ref 7b.

(25) Our assignment of the stereochemistry of synthetic **3** is based on (a) a single-crystal X-ray analysis of **31a** using the Flack method for absolute stereochemistry and (b) the expected stereochemistry from the sequence of reactions that transformed alcohol **14a** to isocyanate **16a** as reported in ref 11b. The diastereomeric purity of alcohol **14a** and isocyanate **16a** was checked against authentic diastereomers made from **14b**. In any case, a loss in enantiomeric purity would not account for a change in the sign of optical rotation.

(26) Their assignment of the absolute stereochemistry of (−)-aspidofractinine **3** is based on comparison of the OCD spectra of *N*-acetylaspidofractinine (+)-**38** obtained from the degradation of minovincine (−)-**2** and from the acetylation of natural aspidofractinine **3** (see scheme below). However, the assignment of the absolute stereochemistry of (−)-**2** is based on a similarity of structure with vindicafformine (−)-**37**. The absolute stereochemistry of natural (−)-**37** has been confirmed by total synthesis but not that of natural (−)-**2**. It is important to note that both (+)-**2** and (−)-**2** exist in nature. For syntheses of (−)-**37**: (a) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172–2183. (b) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924–929. For the isolation of (−)-**2**: (c) Douzoua, L.; Mansour, M.; Bebray, M. M.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1974**, *13*, 1994–1995. (d) Meisel, H.; Doepke, W. *Tetrahedron Lett.* **1970**, 749–751. For the isolation of (+)-**2**: (e) Cava, M. P.; Tjoa, S. S.; Ahmed, Q. A.; Da Rocha, A. I. *J. Org. Chem.* **1968**, *33*, 1055–1059. (f) Liu, G.; Liu, X.; Feng, X. *Planta Med.* **1988**, *54*, 519–521.



SCHEME 9



solid (4.0 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30 (d, 1H, J = 7.6 Hz), 7.00 (t, 1H, J = 7.6 Hz), 6.78 (t, 1H, J = 7.6 Hz), 6.64 (d, 1H, J = 7.6 Hz), 3.24 (q, 1H, J = 8.8 Hz), 3.11 (s, 1H), 3.15−2.60 (m, 4H), 2.72 (ddd, 1H, J = 13.7, 8.8, 3.3 Hz), 2.28−2.10 (m, 2H), 1.92−1.61 (m, 4H), 1.52 (br d, 1H, J = 13.7 Hz), 1.45−1.39 (m, 1H), 1.34−1.18 (m, 5H); NMR spectrum was identical to those previously published;[3,7b,24] $[\alpha]^{20}_D$ = +12 (c = 0.27, $CHCl_3$).

Allylic Alcohol 14a. 2-Allyl-1-benzenesulfonyl-3-(2,2-dibromovinyl)indole **11a** (4.80 g, 9.97 mmol) was dissolved in THF (100 mL), and the solution was cooled to −95 °C. NaHMDS (1 M in THF, 15.0 mL, 15.0 mmol) was added dropwise. The reaction was stirred at −95 °C during 10 min. A solution of *n*-BuLi in hexane (2.35 M, 8.48 mL, 19.9 mmol) was added dropwise. The reaction was stirred at −95 °C during 10 min. *p*-Menthane-3-carboxaldehyde **8** (2.01 mL, 12.0 mmol) was dissolved in THF (40 mL) and added dropwise. The mixture was stirred at −95 °C during 10 min and then quenched with methanol (5.0 mL) at that temperature. After allowing the mixture to warm to rt, saturated NH_4Cl solution and the mixture were warmed to rt. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give yellow oil. The crude mixture of propargylic alcohols was dissolved in THF (150 mL), and the solution was cooled to 0 °C. Red-Al (65% w/w in toluene, 6.82 g, 21.9 mmol) was added dropwise. The reaction was stirred at rt for 15 min. The reaction mixture was quenched with brine. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography on a silica gel column eluting with hexanes and ethyl acetate (9:1) to give allylic alcohols **14a** (3.47 g, 71%) and **14b** (977 mg, 20%) both as a colorless oil. Major isomer **14a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, 1H, J = 7.2, 2.4 Hz), 7.76 (d, 2H, J = 7.6 Hz), 7.72 (dd, 1H, J = 7.2, 2.4 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.37 (t, 2H, J = 7.6 Hz), 7.33−7.27 (m, 2H), 6.63 (dd, 1H, J = 16.0, 1.1 Hz), 6.32 (dd, 1H, J = 16.0, 5.1 Hz), 6.01 (ddt, 1H, J = 17.0, 9.6, 5.8 Hz), 5.06 (d, 1H, J = 9.6 Hz), 5.02 (dd, 1H, J = 17.0, 1.65 Hz), 4.66 (d, 1H, J = 5.1 Hz), 3.91 (d, 2H, J = 5.8 Hz), 2.20 (dqi, 1H, J = 6.6, 2.8 Hz), 1.85−1.66 (m, 2H), 1.72 (d, 2H, J = 11.6 Hz), 1.47 (q, 1H, J = 11.2 Hz), 1.43−1.22 (m, 2H), 1.13−0.78 (m, 2H), 0.97 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz), 0.82 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 138.9 (s), 136.7 (s), 135.7 (d), 135.6 (s), 134.8 (d), 133.7 (d), 129.1 (d), 128.8 (s), 126.4 (d), 124.6 (d), 123.8 (d), 119.8 (d), 119.6 (d), 119.3 (s), 116.4 (t), 115.0 (d), 71.9 (d), 44.8 (d), 43.1 (d), 35.1 (t), 34.1 (t), 32.8 (d), 30.2 (t), 26.4 (d), 24.3 (t), 22.8 (q), 21.6 (q), 15.5 (q); IR (neat) ν (cm^{-1}) 3642−3241, 3069, 1450, 1367; LRMS (m/z, relative intensity) 491 (M^+, 20), 352 (100); HRMS calcd for $C_{30}H_{37}NO_3S$ 491.2494, found 491.2489; $[\alpha]^{20}_D$ = −11.3 (c = 1.95, $CHCl_3$); %de pure product >99% (HPLC).

***O*-Carbamate 15a.** Allylic alcohol **14a** (3.47 g, 7.60 mmol) was dissolved in THF (75 mL), and the solution was cooled to 0 °C. Trichloroacetylisocyanate (2.00 g, 10.6 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h. THF was then evaporated from the reaction mixture, and methanol (35 mL) was added to the residue. The mixture was cooled to 0 °C; an aqueous saturated solution of K_2CO_3 (5 mL) was added portionwise, and the mixture was then stirred for 30 min at 0 °C and at rt for 1 h. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The organic layers were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography on a silica gel column eluting with hexanes and ethyl acetate (7:3) to give allylic carbamate as a colorless oil **15a** (3.61 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21 (dd, 1H, J = 6.9, 2.5 Hz), 7.74 (d, 2H, J = 7.7 Hz), 7.69−7.64 (m, 1H), 7.56−7.48 (m, 1H), 7.39 (t, 2H, J = 7.7 Hz), 7.34−7.24 (m, 2H), 6.54 (dd, 1H, J = 16.2, 1.1 Hz), 6.19 (dd, 1H, J = 16.2, 5.8 Hz), 5.99 (ddt, 1H, J = 16.9, 10.2, 6.0 Hz), 5.53 (d, 1H, J = 5.8 Hz), 5.06 (dd, 1H, J = 10.2, 1.4 Hz), 5.02 (dd, 1H, J = 16.9, 1.4 Hz), 4.60 (br s, 2H), 3.87 (d, 2H, J = 6.0 Hz), 2.15 (m, 1H), 1.83−1.63 (m, 3H), 1.63−1.49 (m, 1H), 1.38−1.17 (m, 3H), 1.09−0.75 (m, 2H), 0.91 (d, 3H, J = 7.1 Hz), 0.87 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.0 (s), 138.9 (s), 136.7 (s), 135.9 (s), 134.8 (d), 133.7 (d), 130.8 (d), 129.2 (d), 128.6 (s), 126.4 (d), 124.6 (d), 123.8 (d), 121.3 (d), 119.7 (d), 119.0 (s), 116.5 (t), 115.0 (d), 75.5 (d), 43.7 (d), 43.2 (d), 35.6 (t), 34.9 (t), 32.7 (d), 30.3 (t), 26.4 (d), 24.1 (t), 22.7 (q), 21.6 (q), 15.4 (q); IR (neat) ν (cm^{-1}) 3550−3100 (br), 1723, 1367; LRMS (m/z, relative intensity) 534 (M^+, 15), 473 (95), 352 (45), 194 (100); HRMS calcd for $C_{31}H_{38}N_2O_4S$ 534.2552, found 534.2542; $[\alpha]^{20}_D$ = −19.7 (c = 1.57, $CHCl_3$).

Trichloroethoxycarbamate 17a. Allylic *O*-carbamate **15a** (7.70 g, 14.4 mmol) was dissolved in DCM (500 mL), and the solution was cooled to 0 °C. Then, Et_3N (6.7 mL, 43.2 mmol) followed by TFAA (2.2 mL, 15.8 mmol) were added over a period of 30 min. The reaction mixture was stirred at 0 °C for 10 min, after which time 2,2,2-trichloroethanol (13.8 mL, 14.4 mmol) was added and the reaction was stirred for 3 h while removing the ice bath and allowing the solution to warm to rt. A saturated solution of aquous $NaHCO_3$ was added, and the phases were separated. The aqueous phase was extracted three times with DCM, the organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by

flash chromatography on a silica gel column eluting with hexanes, DCM, and ethyl acetate (17:2:1) to give allylic carbamate **17a** as a colorless oil (9.4 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21 (d, 1H, J = 7.6 Hz), 7.74 (d, 2H, J = 7.6 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.47 (d, 1H, J = 7.6 Hz), 7.40 (t, 2H, J = 7.6 Hz), 7.30 (t, 1H, J = 7.6 Hz), 7.22 (t, 1H, J = 7.6 Hz), 5.98 (ddt, 1H, J = 16.8, 9.9, 5.2 Hz), 5.65−5.53 (m, 2H), 5.65−5.53 (m, 2H), 5.40 (d, 1H, J = 7.1 Hz), 5.31 (dd, 1H, J = 14.2, 9.4 Hz), 5.03 (d, 1H, J = 9.9 Hz), 4.99 (d, 1H, J = 16.8 Hz), 4.76 (d, 1H, J = 12.1 Hz), 4.59 (d, 1H, J = 12.1 Hz), 4.00 (dd, 1H, J = 16.5, 5.2 Hz), 3.90 (dd, 1H, J = 16.5, 5.2 Hz), 1.98−1.84 (m, 1H), 1.78−1.50 (m, 3H), 1.41−1.18 (m, 2H), 1.02−0.71 (m, 2H), 0.85 (d, 3H, J = 6.6 Hz), 0.76 (d, 3H, J = 7.1 Hz), 0.61 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.7 (s), 138.9 (s), 137.9 (d), 136.8 (s), 136.1 (s), 135.2 (d), 133.7 (d), 129.2 (d), 127.9 (s), 126.4 (d), 126.4 (d), 124.5 (d), 123.4 (d), 120.3 (s), 119.7 (d), 116.6 (t), 115.4 (d), 95.6 (s), 74.4 (t), 49.1 (d), 47.0 (d), 44.3 (d), 42.8 (t), 35.1 (t), 32.4 (d), 30.0 (t), 28.0 (d), 24.0 (t), 22.8 (q), 21.5 (q), 15.5 (q); IR (neat) ν (cm^{-1}) 3475−3208 (br), 1734, 1721; LRMS (m/z, relative intensity) 664 (M^+, 1), 474 (40), 377 (50), 230 (70), 194 (100); HRMS calcd for $C_{33}H_{39}N_2O_4SCl_3$ 664.1696, found 664.1702; $[\alpha]^{20}_D$ = −40.2 (c = 1.10, $CHCl_3$); dr 11:1 (HPLC).

Pentacyclic Compound 31a. $[Cu(OTf)]_2 \cdot$ toluene (22 mg, 0.043 mmol) was dissolved in DCM (20 mL). The diazo compound **30** (94 mg, 0.200 mmol) diluted in 20 mL of DCM was added to the reaction mixture over 4 h with a syringe pump. The reaction was stirred at rt for 30 min. The reaction mixture was concentrated, and the crude product was purified by flash chromatography on a silica gel column eluting with hexanes and EtOAc (1:1) to give the product **31a** as a white solid (68 mg, 76%): mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.90 (d, 2H, J = 7.5 Hz), 7.75 (d, 1H, J = 7.5 Hz), 7.61 (t, 1H, J = 7.5 Hz), 7.52 (d, 2H, J = 7.5 Hz), 7.26 (t, 2H, J = 7.5 Hz), 7.06 (t, 1H, J = 7.5 Hz), 6.22 (ddd, 1H, J = 9.4, 6.5, 1.9 Hz), 6.08 (ddd, 1H, J = 9.4, 5.5, 3.3 Hz), 4.70 (d, 1H, J = 6.5 Hz), 3.60−3.44 (m, 4H), 2.92 (ddd, 1H, J = 13.7, 7.4, 6.0 Hz), 2.44 (ddd, 1H, J = 19.2, 3.3, 2.2 Hz), 2.07 (m, 1H), 1.98 (sept, 1H, J = 7.1 Hz), 0.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 169.3 (s), 143.2 (s), 136.8 (s), 134.0 (d), 133.4 (d), 129.4 (d), 128.4 (d), 128.4 (s), 127.7 (d), 124.8 (d), 123.9 (d), 1.3 (d), 115.4 (d), 51.8 (s), 50.3 (d), 42.3 (t), 40.5 (s), 38.9 (t), 32.2 (d), 30.1 (t), 28.9 (t); IR (neat) ν (cm^{-1}) 3055, 1682, 1362; LRMS (m/z, relative intensity) 440 (M^+, 5), 299 (75), 180 (100); HRMS calcd for $C_{23}H_{21}N_2O_3SCl$ 440.0961, found 440.0970; $[\alpha]^{20}_D$ = −96.2 (c = 1.25, $CHCl_3$).

Enimine 34. Compound **33** (110 mg, 0.413 mmol) was dissolved in THF (30 mL) and pyridine (5 mL). Phenylseleninic acid (234 mg, 1.24 mmol) was added, and the mixture was heated to reflux for 30 min. The mixture was cooled to rt, brine was added, and the phases were separated. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography on a silica gel column starting with EtOAc and going to a mixture of EtOAc and MeOH (19:1) to give the product **34** as a white solid (67 mg, 61%): ^{1}H NMR (300 MHz, C_6D_6) δ (ppm) 7.65 (d, 1H, J = 7.4 Hz), 7.08 (t, 1H, J = 7.4 Hz), 6.95 (t, 1H, J = 7.4 Hz), 6.79 (d, 1H, J = 7.4 Hz), 6.52 (dd, 1H, J = 10.0, 3.0 Hz), 5.40 (dt, 1H, J = 10.0, 1.9 Hz), 4.27 (m, 1H), 3.35 (dd, 1H, J = 5.5, 1.1 Hz), 2.48 (d, 1H, J = 17.9 Hz), 2.34 (d, 1H, J = 17.9 Hz), 2.24 (m, 1H), 1.49−1.40 (m, 1H), 1.32−1.05 (m, 2H), 1.03−0.79 (m, 2H); the ^{1}H NMR spectral data in $CDCl_3$ were identical to that reported in the literature;[7d] IR (neat) ν (cm^{-1}) 3042, 1695, 1452; LRMS (m/z, relative intensity) 264 (M^+, 100), 180 (30); HRMS calcd for $C_{17}H_{16}N_2O$ 264.1263, found 264.1259; $[\alpha]^{20}_D$ = +39.2 (c = 1.06, C_6H_6).

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Supporting Information Available: Experimental procedures for all new compounds not included in the Experimental Section, ^{1}H NMR spectra for all new compounds, and X-ray tables and data for compound **31a**. This material is available free of charge via the Internet at http://pubs.acs.org.