Design and Implementation of an Efficient Synthetic Approach to Furanosylated Indolocarbazoles: Total Synthesis of (+)- and (−)-K252a

John L. Wood,* Brian M. Stoltz, Hans-Jürgen Dietrich, Derek A. Pflum, and Dejah T. Petsch

Contribution from the Sterling Chemistry Laboratory, Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

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Abstract: The first total synthesis of the natural product (+)-K252a (**2**) has been achieved in 12 steps from commercially available materials, with a longest linear sequence of seven steps and an overall yield of 21%. The synthetic strategy employs novel rhodium carbenoid chemistry in the construction of both the indolocarbazole aglycon (**4**) and the carbohydrate moiety (**9**).

In 1977 Ōmura and co-workers reported that a novel alkaloid, isolated from *Streptomyces staurosporeus*, possessed strong hypotensive properties as well as broad spectrum antifungal activity.[1] The structure of this alkaloid, originally termed AM-2282 (**1**), was elucidated by single-crystal X-ray analysis and shown to possess an indolocarbazole subunit wherein the two indole nitrogens are bridged by glycosyl linkages.[2] Following the structure elucidation, AM-2282 was renamed staurosporine, the first of over 50 alkaloids that have since been isolated and are characterized by the indolo[2,3-*a*]carbazole subunit.[3] In 1985, Sezaki reported the isolation and structure of a furanosylated indolocarbazole, SF-2370 (**2**).[4] A year later, Kase described the isolation and complete structure elucidation of K252a, a compound that proved identical to SF-2370, along with three structurally related compounds K252b−d (**3**−**5**, Figure 1).[5] Kase found these compounds to be potent inhibitors of protein kinase C (PKC), with K252a possessing the greatest inhibitory power (IC$_{50}$ = 32 nM). In the same year, Tamaoki reported that staurosporine also inhibits PKC but with a slightly higher affinity (IC$_{50}$ = 2.7 nM).[6] Following the discovery of potent kinase inhibitory activity, the indolocarbazoles rapidly became the focus of several investigations that have revealed their potential as chemotherapeutics against cancer,[7] Alzheimer's disease,[8] and other neurodegenerative disorders.[9]
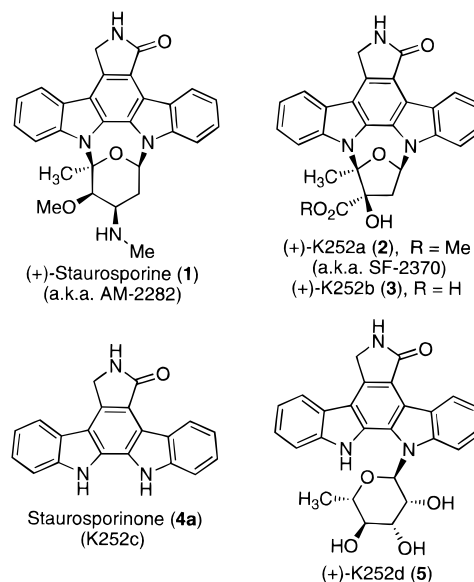

Figure 1.

Previous Synthetic Work. The important biological activity and novel structures of **1** and **2** have inspired an intense 14 year effort by synthetic chemists to develop efficient methods for accessing the indolocarbazole nucleus and respective carbohydrate moieties. At the outset of our investigations, five syntheses had been reported for the aglycon (K252c, **4a**) as well as a number of reports for the preparation of protected variants and closely related derivatives.[10−12] In contrast, only two approaches had been developed for the preparation of a

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

(1) For the isolation of (+)-staurosporine, see: Ōmura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275.

(2) (a) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Ōmura, S. *J. Chem. Soc., Chem. Commun.* **1978**, 800. (b) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Ōmura, S. *Bull. Chem. Soc. Jpn.* **1982**, *5*, 3681. (c) In the course of our synthetic endeavors, the absolute stereochemical configuration of staurosporine was determined by X-ray analysis; see: Funato, N.; Takayanagi, H.; Konda, Y.; Toda, Y.; Harigaya, Y.; Iwai, Y.; Ōmura, S. *Tetrahedron Lett.* **1994**, *35*, 1251.

(3) For reviews on the synthesis and biological activity of indolocarbazoles, see: (a) Bergman, J. *Stud. Nat. Prod. Chem., Part A* **1988**, *1*, 3. (b) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.* **1993**, *12*, 365. (c) Steglich, W. *Fortschr. Chem. Org. Naturst.* **1987**, *51*, 216. (d) Ōmura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.

(4) Sezaki, M.; Sasaki, T.; Nakazawa, T.; Takeda, U.; Iwata, M.; Watanabe, T.; Koyama, M.; Kai, F.; Shomura, T.; Kojima, M. *J. Antibiot.* **1985**, *38*, 1437.

(5) (a) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059. (b) Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1066. (c) Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, N.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *39*, 1072.

(6) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.

(7) For a comprehensive review, see ref 3d.

(8) (a) Masliah, E.; Cole, G. M.; Hansen, L. A.; Mallory, M.; Albright, T.; Terry, R. D.; Saitoh, T. *J. Neurosci.* **1991**, *11*, 2759. (b) Gandy, S.; Czernik, A. J.; Greengard, P. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6218.

(9) For a recent review, see: Knüsel, B.; Hefti, F. *J. Neurochem.* **1992**, *59*, 1987.

(10) For approaches that deliver an intact and fully deprotected aglycon (i.e., **4a**), see: (a) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469. (b) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475. (c) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1667. (d) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105. (e) Toullec, D.; Pianetti, P.; Coste, H.; Bellevergue, P.; Grand-Perret, T.; Ajakane, M.; Baudet, V.; Boissin, P.; Boursier, E.; Loriolle, F.; Duhamel, L.; Charon, D.; Kirilovsky, J. *J. Biol Chem.* **1991**, *266*, 15771. (f) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361. (g) Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555.

Scheme 1

8a R = H
8b R = CO$_2$Me
1:1 mixture
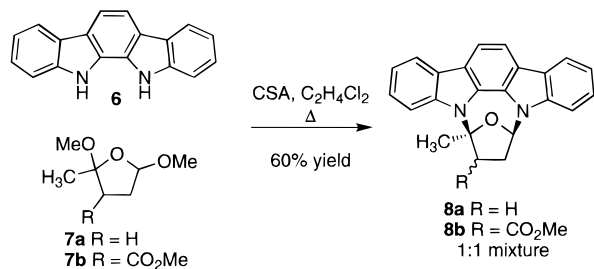
carbohydrate slated for use in the synthesis of a bis-glycosylated indolocarbazole, both targeted staurosporine.[13b,14a]

In addition to the carbohydrate efforts, three groups had reported protocols for the bis-indole-*N*-glycosidic coupling of indolocarbazoles.[13–16] For the pyranosylation of the indolocarbazole nucleus, a low-yielding two-step acid-catalyzed procedure was developed by McCombie.[14b] Danishefsky and Link developed landmark protocols for multistep pyranosylation that rely on successive indolyl glycosidation by endo and exo glycals.[14a,c] A variant of this was recently employed in the first total synthesis of (+)- and (−)-staurosporine.[17] For the preparation of furanosylated indolocarbazoles, the viability of a single-step acid-promoted coupling to form both glycosidic linkages had been demonstrated in early investigations by Weinreb[13a,b] and later refined by McCombie (i.e., **6** + **7a** → **8a**, Scheme 1).[13c] Although the single-step furanosylation appeared efficient, early reports that more fully functionalized carbohydrates such as **7b** resulted in high yields of coupled products, but as a mixture of diastereomers **8b**, left the practicality of such an approach in question.

K252a Retrosynthetic Analysis.[18,19] In planning a synthesis of K252a, we viewed the single-step cycloglycosidation as the

(11) For an approach to **4a** that involves the degradation of rebeccamycin, see: (a) Fabre, S.; Prudhomme, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 449. (b) Fabre, S.; Prudhomme, M.; Rapp, M. *Bioorg. Med. Chem.* **1993**, *1*, 193. (c) Fabre, S. Prudhomme, M.; Sancelme, M.; Rapp, M. *Bioorg. Med. Chem.* **1994**, *2*, 73.

(12) For approaches that deliver an intact and protected aglycon but fail to demonstrate the feasibility of deprotection, see the following. (a) *N*-Protected indole: Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795. Brüning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25. (b) *N*-Protected indole and amide: Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 9135. Winterfeldt, E. In *Heterocycles in Bioorganic Chemistry*; Bergman, J., Ed.; The Royal Society of Chemistry: London, 1991. (c) *N*-Protected amide: Hughes, I.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 1441. Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.

(13) For examples of single-step cyclofuranosylations of indolocarbazoles, see: (a) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309. (b) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177. (c) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirschmeier, P.; Lin, S.-I.; Petrin, J.; Rosinski, K.; Shankar, B. B.; Wilson, O. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1537.

(14) For the construction of pyranosylated indolocarbazoles possessing two indole-*N*-glycosidic bonds, see: (a) Link, J. T.; Gallant, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 3782. (b) Shankar, B. B.; McCombie, S. W. *Tetrahedron Lett.* **1994**, *35*, 3005. (c) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552.

(15) For the total synthesis of rebeccamycin, a pyranosylated indolocarbazole possessing a single indole-*N*-glycosidic linkage, see: (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015. (b) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.

(16) Recently, an elegant and selective monoglycosidation approach was developed for 2,2′-indolylindolines; see: (a) Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1995**, *60*, 6672. (b) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500.
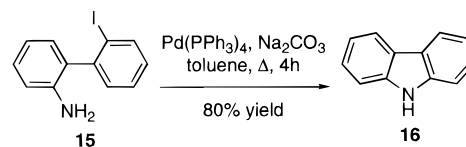
(17) For a full-account of the Danishefsky–Link synthesis of staurosporine, see: Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.

(18) Recently, we reported the synthesis of (+)- and (−)-K252a in a communication; see: Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.

Scheme 2
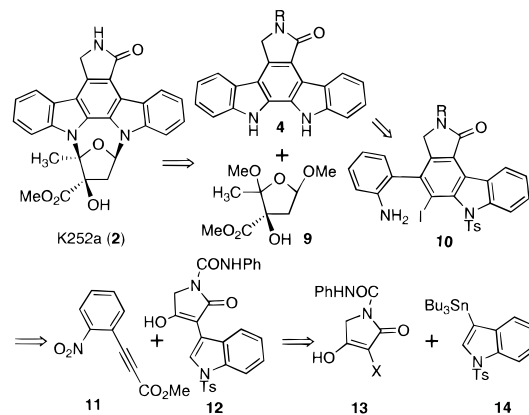
Scheme 3

most efficient approach (i.e., **2** ⇒ **4** + **9**, Scheme 2), especially if the regio- and stereochemical issues associated with coupling a fully functionalized furanose could be addressed. Thus, we based our synthetic design on this most simplifying disconnection and began considering the preparation of a selectively protected aglycon (e.g., **4**, R = protective group) and an appropriate furanose (e.g., **9**). Although several of the known approaches to **4a** (R = H) could possibly have been modified to deliver protected derivatives, we sought to develop a novel protocol that would be both efficient and amenable to installing a variety of protecting groups at the lactam nitrogen. We viewed the latter as a particularly important design feature given the likelihood of having to screen the suitability of several protecting groups.[20]

Synthesis of K252c (4a): A First-Generation Approach. With several design features in mind, a first-generation strategy toward **4** emerged (Scheme 2). This approach called for late-stage cyclofuranosylation (e.g., **4** + **9** → **2**) and palladium-mediated C−N bond formation in the carbazole synthesis (e.g., **10** → **4**). Diels−Alder cycloaddition of indolepyrrolidone **12** with acetylene **11** was envisioned to be the first critical step. As a prelude to this approach, the carbazole-forming reaction was investigated rather extensively in a model system (Scheme 3). In accord with Migita's protocol, we initially explored a tin amide (RNHSnBu$_3$) as the substrate;[21] however, under certain conditions ring closure occurred in the absence of tin.[22] Thus, carbazole could be produced in up to 80% yield (e.g., **15**[23] → **16**) using Pd(PPh$_3$)$_4$ (1.1 equiv), Na$_2$CO$_3$ in toluene at reflux for 4 h. Reactions employing catalytic amounts of Pd (5 mol %) resulted in the formation of carbazole (ca. 60%) but only after prolonged reaction periods (5 days).[24]

(19) An independent approach to (±)-**2** was reported shortly after our initial communication; see: Lowinger, T. B.; Chu, J.; Spence, P. L. *Tetrahedron Lett.* **1995**, *36*, 8383.

(20) On the basis of a report by Raphael[10b] that a benzyl protecting group could not be removed from the lactam nitrogen, it seemed wise to proceed in this most general manner.

(21) For the palladium-catalyzed cross coupling of aryl halides with tin amides, see: Kosugi, M.; Kameyama, M.; Migita, T. *Chem Lett.* **1983**, 927.
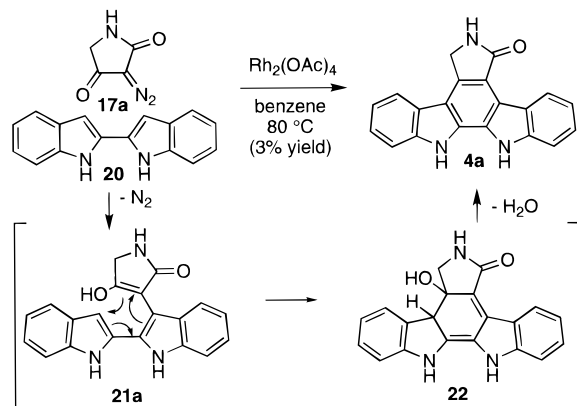
(22) A similar Pd(0)-mediated ring closure has been developed for the preparation of the β-carboline skeleton; see: Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(23) For the preparation of 2-(2-iodophenyl)aniline (**15**), see: Cade, J. A.; Pilbeam, A. *J. Chem. Soc.* **1964**, 114.

Scheme 4
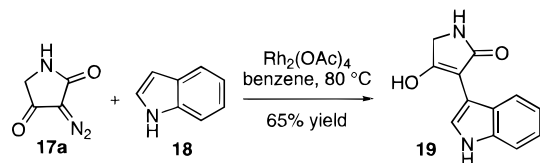
Scheme 5

Scheme 6

Scheme 7

Having established the feasibility of forming a carbazole using Kosugi's reaction, we turned toward preparing the actual substrate **4** and began investigating an approach to diene **12** that called for coupling of indole **14**[25] to a halopyrrolidone **13** (X = Br, I).[26] Unable to effect the Stille coupling of **13** and **14**, we began considering alternative strategies and were drawn to a report from 1935 describing the preparation of ethyl 3-indoleacetate via coupling of indole with ethyl diazoacetate in the presence of Cu metal.[27] In investigating this as an approach to **12** we discovered that known diazotetramic acid **17a**[28] undergoes smooth conversion to the elusive diene **19** when exposed to $Rh_2(OAc)_4$ and indole (**18**) in benzene at reflux (65% yield, Scheme 4).[29]

However, difficulties encountered in advancing diene **19** to carbazole **10** via our Diels−Alder strategy led us to reconsider the approach. Eventually we recognized that a similar diazo addition reaction, using 2,2′-biindole as substrate, might produce a product that, upon electrocyclization/dehydration, would furnish K252c directly (e.g., **17a** + **20** → **4a**, Scheme 5).[30]

Synthesis of K252c (4a): Second-Generation Approach. In accord with the revised plan, we prepared 2,2′-biindole (**20**) from **23** via a double Madelung cyclization, an excellent procedure recently published by Bergman (Scheme 6).[30f] Initial attempts to implement this revised approach by combining diazo lactam **17a** with **20** under conditions identical to those used for

the preparation of **19** produced trace amounts of a substance possessing ^{1}H NMR resonances in accord with K252c. Given this glimmer of hope, we expended considerable effort optimizing the reaction. Guided by the observation of what appeared to be benzene C−H insertion products and the fact that **20** appeared only sparingly soluble in benzene, we began screening several nonreactive solvents. In the event, we discovered that solvents typically employed in rhodium carbenoid reactions (i.e., chloroform, methylene chloride, hexafluorobenzene, 1,2-dichloroethane, xylenes, toluene, and chlorobenzene) all poorly dissolved the substrate. However, when less traditional solvents such as ethyl acetate and acetone were employed, a striking increase in the amount of substrate solubility was noticed along with an appreciable increase in the production of **4a** to 15%. Reasoning that the carbenoid may be interacting unfavorably with the medium (e.g., carbonyl ylide formation), we explored the use of more sterically encumbered carbonyl-containing solvents. In addition, observations that exposure to air resulted in darkening of the reaction mixture led us to implement more rigorous deoxygenation methods. In the end, changing the solvent to pinacolone and degassing with N_2 prior to reaction in a sealed tube at 120 °C had a profound effect on the yield of K252c (now isolated in 25% yield).

Further Successful Carbenoid Additions to 2,2′-Biindole: Completion of 4b−e. As shown in Scheme 7, a series of diazo compounds were prepared by the procedure used to produce **17a**. Thus, *N*-substituted glycine esters **24b−e**,[31] were exposed to DCC/DMAP-promoted coupling with ethyl hydrogen malonate followed by Dieckmann cyclization (NaOEt/EtOH) to produce lactams **25b−e**. A single-pot decarboethoxylation/diazo-transfer reaction was effected by heating **25b−e** in wet acetonitrile and then treating the cooled reaction mixture (0 °C) with MsN_3 and triethylamine. The overall process involves a single purification step, can be conveniently carried out on a 20 g scale, and results in an approximate 50% overall yield of diazo lactams **17b−e** from **24b−e**.

With ample quantities of lactams **17b−e** and biindole **20** readily available, we applied our optimized reaction conditions. To our delight, introduction of the amide protecting group

(24) Recently, Buchwald developed improved procedures for this type of aryl amination; see; Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

(25) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, 831.

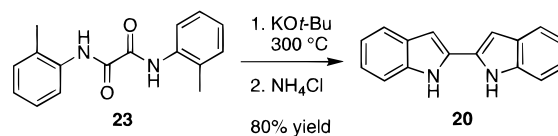(26) Gerike, P. U.S. Patent 3 541 111, 1970; *Chem. Abstr.* **1971**, *74*, 99861u.

(27) Jackson, R. W.; Manske, R. H. *Can. J. Res.* **1935**, *13*, 170.

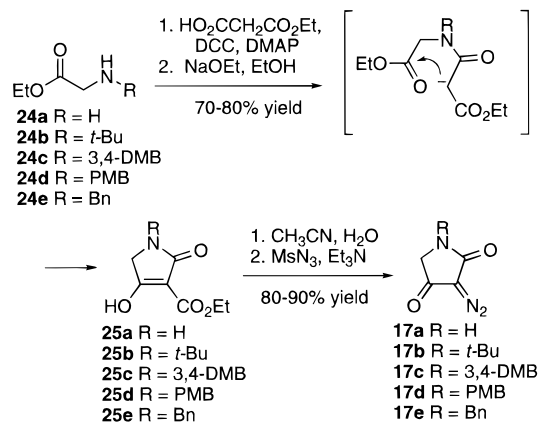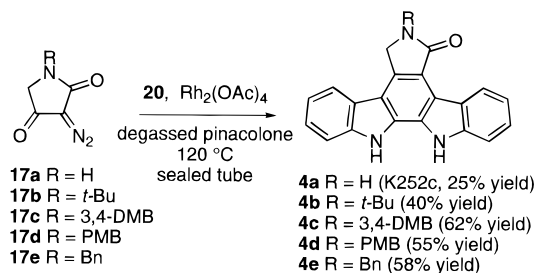(28) Lowe, G.; Yeung, H. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2907.

(29) Pirrung has reported the 1,3 dipolar cycloaddition of a diazo ketone with *N*-acetylindole; see: Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112.

(30) In terms of substrates, this approach is similar to attempted Diels−Alder reactions between maleimides and biindole **20**. These efforts have met with limited success; see: (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015. (b) Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285. (c) Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *Heterocycles* **1994**, *38*, 2267. (d) Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *J. Heterocycl. Chem.* **1994**, *31*, 377. (e) Barry, J. F.; Wallace, T. W.; Walshe, N. D. A. *Tetrahedron Lett.* **1993**, *34*, 5329. (f) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631. (g) Barry, J. F.; Wallace, T. W.; Walshe, N. D. A. *Tetrahedron* **1995**, *51*, 12797.

(31) Protected glycine esters were prepared according to known literature procedures; see: (a) Mannich, C.; Kuphal, R. *Chem. Ber.* **1912**, *45*, 314. (b) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225.

Scheme 8

17a R = H
17b R = *t*-Bu
17c R = 3,4-DMB
17d R = PMB
17e R = Bn

4a R = H (K252c, 25% yield)
4b R = *t*-Bu (40% yield)
4c R = 3,4-DMB (62% yield)
4d R = PMB (55% yield)
**4e** R = Bn (58% yield)
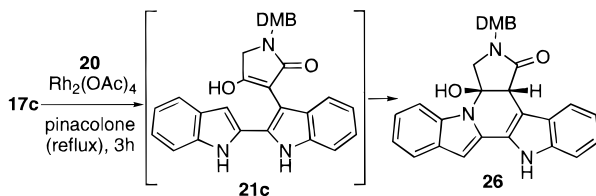
Scheme 9

appeared to favorably influence the yield, particularly in substrates possessing benzyl-type protecting groups (Scheme 8). The optimized sequence is highlighted by preparation of the 3,4-dimethoxybenzyl-protected aglycon **4c**, which was produced in 62% yield (50% overall yield for the three steps from *o*-toluidine)!

In these initial studies, reactions had been performed on approximately 100 mg of **20** in a sealed tube at elevated temperature using 10 mol % Rh$_2$(OAc)$_4$ and 3−4 equiv of the diazo lactam (i.e., **17c**). For the purposes of the K252a synthesis, this scale was quite suitable; however, since extending this effort to staurosporine was expected to require multigram quantities of **4c**,[32] we continued our optimization efforts. To this end, we attempted the reaction at atmospheric pressure and reduced the stoichiometry of the Rh(II) catalyst and diazo substrate. In the event, reaction of biindole **20**, diazo lactam **17c** (1:1 mol equiv), and Rh$_2$(OAc)$_4$ (1.0 mol %) in degassed pinacolone at reflux for 8 h produced a 36% yield of protected aglycon (72% yield based on recovered biindole). Typically this reaction is run on 4.0 g of **20** and produces 2.9 g of **4c**. In the course of developing this improved multigram procedure, a second isolable product was observed (ca. 5−10% yield) which, upon either heating in xylenes at reflux or exposure to CSA, undergoes quantitative conversion to **4c**. Tentatively assigned as **26** based on spectral data (Scheme 9), this product likely forms from the initial adduct (**21c**) and supports our speculation of the stepwise process outlined in Scheme 5.

Preparation of the K252a Carbohydrate (±)-9. Prior to our investigations, there were no reported syntheses of the K252a carbohydrate. Viewing (±)-**9** in an open-chain form reveals keto aldehyde **27** and clearly presents methyl acetoacetate as an exploitable intermediate (Scheme 10). Thus, our initial approach to (±)-**9** began with the Pb(OAc)$_4$-mediated oxidation of methyl acetoacetate (**28**),[33] followed by prenylation to produce **29** (31% yield, two steps). Interestingly, reductive ozonolysis and acid-promoted ring closure produced only two of the four expected diastereomeric furanose products. Single-crystal X-ray analysis unambiguously established the structures to be C(5′) epimers **30a** and **30b**.[34] Removal of the acetate provided the cycloglycosidation substrate (±)-**9**. Although not

Scheme 10

(±)-**30a** α-5'-OMe, R = Ac
(±)-**30b** β-5'-OMe, R = Ac
(±)-**9a** α-5'-OMe, R = H
(±)-**9b** β-5'-OMe, R = H
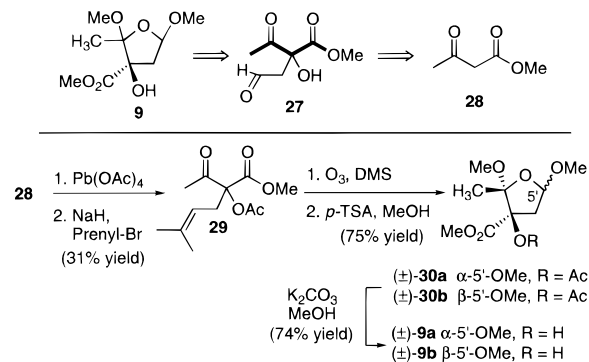
useful in the asymmetric synthesis, this approach was amenable to scale-up and allowed rapid access to gram quantities of the furanose mixture.

Total Synthesis of (±)-K252a. With ample quantities of the K252a carbohydrate and protected aglycons in hand, we began investigating the cycloglycosidation. In an initial attempt, the coupling reaction was performed with K252c (**4**) and (±)-**9** in the presence of CSA as catalyst. The result was formation of a complex mixture comprised in part of products derived from lactam alkylation, thus prompting our exploration of the amide-protected series **4b**−**e**.[35] Given that strong evidence in the literature suggested a simple benzyl group would be resistant to cleavage, we chose to proceed with the 3,4-dimethoxybenzyl-protected aglycon **4c** (Scheme 11). In the event, slow addition of (±)-**9** (2 equiv, 24 h) to a solution of **4c** and CSA (0.1 equiv) in 1,2-dichloroethane at reflux, rapidly produced a quaternary mixture [(±)-**31** and (±)-**32**, *vide infra*] which, quite remarkably, upon prolonged heating was reduced to a 2:1 binary mixture. Following isolation and characterization, the products were determined to be the regioisomeric furanosylated indolocarbazoles (±)-**33** and (±)-**34**; thus, this reaction proceeds stereoselectively such that the C(3′) hydroxyl is oriented syn to the indolocarbazole moiety.[36] Furthermore, the major regioisomer corresponded to the protected K252a derivative (±)-**33**.[37]

In an effort to understand the unexpected and remarkable stereoselectivity of this reaction, we attempted to isolate and characterize the components of the initially formed quaternary mixture. Despite numerous crystallization and chromatographic attempts, we were only able to separate the mixture into two fractions. Isolated in a 2:1 ratio, these fractions were found to be regioisomers **31** and **32**; each was isolated as a 1:1 mixture of what appeared spectroscopically to be open-chain monoamino acetal diastereomers.[38] To support this structural assignment, we investigated the coupling of (±)-**9** with carbazole (**16**) under identical conditions and found that this reaction produces a separable binary mixture wherein each component possesses spectral properties consistent with an open-chain monoamino acetal diastereomer (i.e., **35**, Scheme 12).[39] Satisfied with the structures assigned to **31** and **32**, we explored the reactivity of the isolated major diastereomeric pair (i.e., **31**) and the derived product (±)-**33**. In the event, re-exposure of **31** to the

(32) See following paper in this issue.
(33) (a) Green, N.; LaForge, F. B. *J. Am. Chem. Soc.* **1948**, *70*, 2812. (b) Dimroth, O.; Schweizer, R. *Chem. Ber.* **1923**, *56*, 1375.
(34) Details regarding the crystallographic analyses have been deposited in the Cambridge Crystallographic database and are included in Supporting Information.

(35) In the actual course of events, these studies paralleled our efforts to optimize the preparation of **4a**−**e**.
(36) The stereochemical assignment was initially based on the chemical shift similarities of the methyl ester singlet in **33** and **34**. McCombie has reported a 0.5 ppm chemical shift difference in the ^{1}H NMR between α and β ester signals in **8b**.
(37) Ultimately, the regio- and stereochemical outcome of the cycloglycosidation was deduced from the fact that the major isomer produces the natural product.
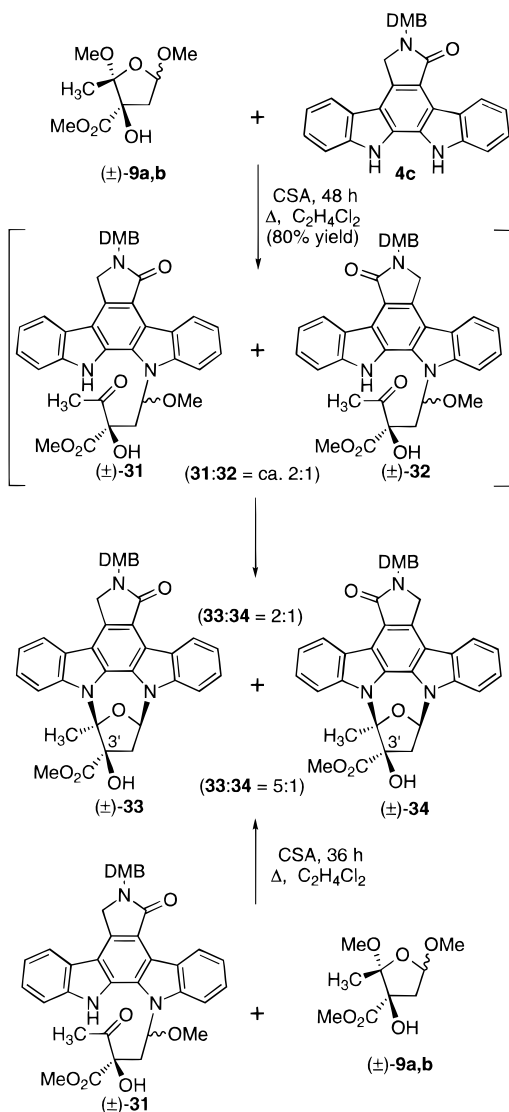(38) The regioisomeric nature of intermediates (±)-**31** and (±)-**32** was determined based on the characteristic free N−H chemical shift difference in the ^{1}H NMR.
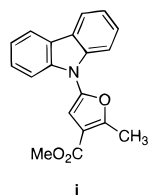
Scheme 11

Scheme 12

cycloglycosidation conditions produced a 5:1 ratio of **33** and **34**, respectively, whereas (±)-**33** remained unchanged under similar conditions; thus, the regioselectivity observed in our initial cycloglycosidation (i.e., **33:34** = 2:1) does not necessarily reflect the thermodynamic stability of **31** and **32**. With regard to stereochemical outcome, the intermediacy of open-chain ketones **31** and **32** indicates that the observed selectivity is

(39) Initially, attempts to cycloglycosidate **4c** with acetates (±)-**30a,b** failed. This result was clarified upon isolation of furan **i** in 53% yield following reaction of carbazole (**16**) with (±)-**30a,b**.


Scheme 13
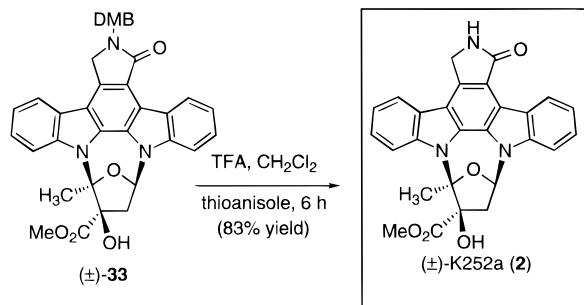
determined in the second step and must be the result of either a kinetic preference in the formation of the furanose oxocarbenium ion or the stability of the possible products to the reaction conditions.[40]

At this stage, removal of the amide protecting group was all that remained for the completion of the synthesis (Scheme 13).[41] Given that the glycosidic linkages had proven quite stable to acid, we turned to conditions originally refined by Steglich for the removal of 2,4-DMB groups from peptides.[42,43] Thus, exposure of (±)-**33** to TFA and thioanisole (cation scavenger)[44,45] in CH_2Cl_2 at 25 °C for a period of 6 h resulted in the clean production of (±)-**2**. The latter proved spectroscopically identical to a sample of the natural material.[46]

Asymmetric Synthesis of Carbohydrate Precursor 41b. Having established **9** to be a suitable synthetic intermediate, we turned our attention toward completing an asymmetric synthesis. Although recent work by Enders indicated that a

(40) Of particular importance to this issue is the stability of the unobserved diastereomer (i.e., **ii**) to the reaction conditions. Unfortunately, the stereoselectivity observed in this reaction made this question impossible to address. However, in a closely related model system the corresponding diastereomer proved stable to these conditions.[32]
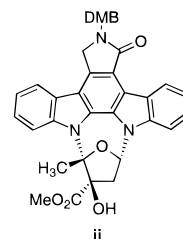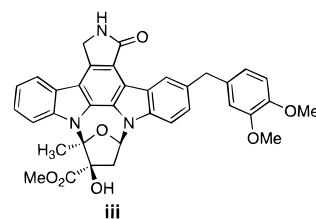

(41) Aglycons **4b,d**, and **e** could be cycloglycosidated with similar results; however, only the products arising from **4d** were successfully deprotected.
(42) Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Khan, N. M. *Tetrahedron Lett.* **1966**, *29*, 3483.
(43) More recently, substituted benzyl amides have been utilized in the tirandamycin area and the 3,4-DMB group was successfully used in a synthesis of the tetrapyrrole pigment precursor porphobilinogen; see: (a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777. (b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219. (c) Jones, M. I.; Froussios, C.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 472.
(44) The well-known tendency of indolocarbazoles to undergo Friedel−Crafts reactions necessitated using a large excess of scavenger. For examples of this Friedel−Crafts reactivity, see: (a) Nakanishi, S.; Yamada, K.; Iwahashi, K.; Kuroda, K.; Kase, H. *Mol. Pharmacol.* **1990**, *37*, 482. (b) Yamada, R.; Sasaki, K.; Omura, S. *Chem. Abstr.* **1991**, *115*, 92688.
(45) In the absence of a cation scavenger, an appreciable amount of **iii** is formed along with (±)-**2**.

(46) We thank the Bayer Corp. for a sample of *nat*-(+)-K252a.

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Scheme 14

Scheme 15

(a) DIBAL, CH_2Cl_2, 0 °C→25 °C,   (b) (*R*)- (+)-α-methoxy-α-(trifluoromethyl)phenylacetic anhydride, DMAP, 25 °C.
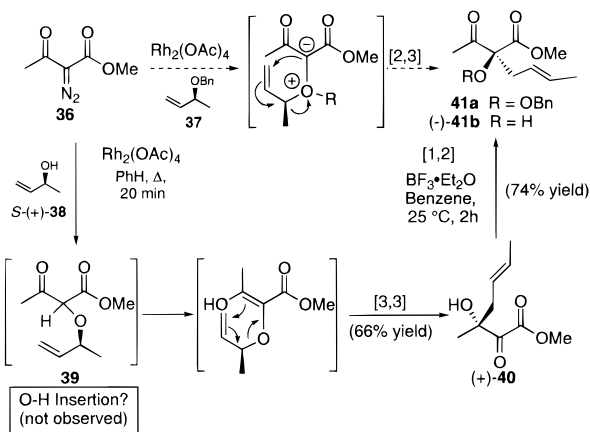
chiral auxiliary controlled version of our approach to **29** would likely be an effective solution to the difficult task of producing the requisite enantioenriched tertiary alcohol,[47] we chose a different course wherein a similar intermediate (i.e., **41a**) was envisioned to arise via [2,3] rearrangement of a chiral carbenoid-derived allyloxonium ion (e.g., **36** + **37** → **41a**, Scheme 14).[48–50] Unfortunately, investigations with benzyl ether **37** and diazo ester **36** produced intractable mixtures. Undaunted, we began to consider alternatives and soon developed a revised plan wherein carbenoid-mediated O–H insertion of a chiral allylic alcohol would serve as the primary event. In this scenario, **41b** was envisioned to arise from the insertion product, an α-allyloxy ketone (e.g., **39**), via a tandem [3,3]/[1,2] rearrangement protocol. From the work of Koreeda we expected that deprotonation of **39** would induce [3,3] rearrangement and produce α-keto ester **40**,[51] a compound that appeared well suited for subsequent Lewis acid-promoted [1,2]-allylic migration.[52] While the bond construction was reasonably well precedented, the issue of stereoselectivity remained speculative. However, given the plethora of rearrangement conditions and Lewis acids, there appeared ample opportunity to influence the stereochemical outcome and we proceeded with the investigation.

In anticipation of isolating α-allyloxy ether **39**, we subjected **36** to rhodium-catalyzed decomposition in the presence of (*S*)-(+)-1-buten-3-ol (**38**).[53] In the event, complete consumption of **36** was observed after only 20 min at reflux in benzene. Proton NMR analysis of the crude reaction indicated the clean formation of a product similar to **39**; however, the characteristic methyl ketone singlet appeared at 1.5 ppm instead of the

(47) For a recent example describing the use of RAMP and SAMP hydrazones in the alkylation of β-keto esters, see: Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Demir, A. S.; Raabe, G. *Chem. Ber.* **1994**, *127*, 1707.

(48) Several excellent reviews have appeared; see: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(49) For a recent review of the [2,3] Wittig rearrangement, see: Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.

(50) The Sharpless kinetic resolution protocol provides a convenient means of accessing a variety of allylic alcohols of very high optical purity; see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(51) (a) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. (b) Examples of both [2,3] and [3,3] rearrangements of α-allyloxy ketones have been reported; see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423 and references therein.

(52) For a leading reference to the Lewis acid-catalyzed α-ketol rearrangement, see: Crout, D. H. G.; Rathbone, D. L. *J. Chem. Soc., Chem. Commun.* **1987**, 290.

(53) This material was prepared from (*S*)-(−)-ethyl lactate; see: Klingler, F. D.; Psiorz, M. German Patent DE-4219510-C1, 1993. Mosher ester analysis (500 MHz ^{1}H NMR) of the derived allylic alcohol established an optical purity of 98% ee.
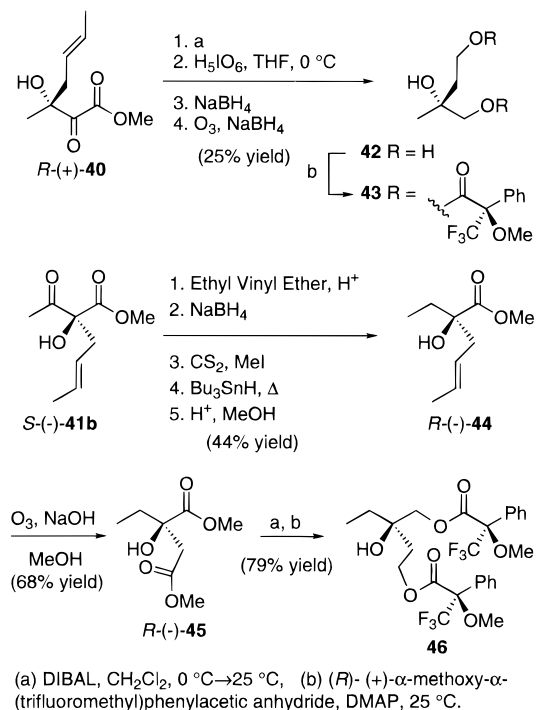
expected 2.2 ppm. Clearly the allyloxy or allyloxonium ylide intermediate had undergone [3,3] sigmatropic rearrangement to alcohol (+)-**40** (66% yield). Completion of the tandem rearrangement protocol was achieved by exposing (+)-**40** to BF_3·OEt_2 which promoted a clean [1,2]-allyl migration to furnish (−)-**41b** in 74% yield. In subsequent studies, improved yields were obtained by conducting the tandem rearrangement in one pot. Thus, introducing 1 equiv of BF_3·OEt_2 into the cooled [3,3] reaction allows isolation of (−)-**41b** in an overall yield of 75%.[54]

With an approach firmly established, we initiated a chemical correlation study to confirm both the sense and degree of asymmetric induction for the tandem rearrangement. Analysis of the purified products from both the [3,3] [i.e., (+)-**40**] and [1,2] [i.e., (−)-**41b**] rearrangements via proton NMR in the presence of Eu(hfc)$_3$ gave the first indication that each step was proceeding with a high degree of stereoselectivity.[55] Conversion of (+)-**40** to **42**[56] as outlined in Scheme 15, followed by comparison of the derived bis Mosher ester (**43**) to samples prepared from (*S*)-(+)- and (*R*)-(−)-citramalic acid, established that (*S*)-(+)-**38** (98% ee) had furnished (*R*)-(+)-**40** (95% ee).[57] Stereoselectivity in the [1,2] shift was established by degradation of (−)-**41b** to (*R*)-(−)-**45**[58] followed by DIBAL reduction and ^{1}H NMR analysis of the corresponding Mosher bisester (**46**).

(54) The dramatic increase in yield over the two-step procedure is attributed to the difficulties of isolating the somewhat volatile products (+)-**40** and (−)-**41b**.

(55) These studies were performed simultaneously in the racemic series.

(56) Compound **42** has been prepared previously from citramalic acid and is of known absolute configuration; see: Gill, M.; Smrdel, A. F. *Tetrahedron Asymmetry* **1990**, *1*, 453.

(57) In the absence of rhodium, one would likely attribute the observed stereochemistry to reaction via a chair transition structure possessing a (*Z*)-enol and an equatorial methyl substituent (i.e., **iv**). However, unpublished results from these laboratories suggest the apparent involvement of rhodium, hence this rationalization may eventually require refinement.

iv
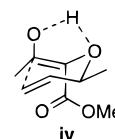
Scheme 16

Scheme 17
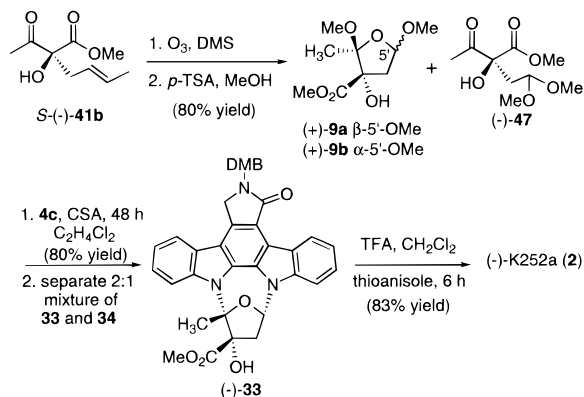
While the Mosher ester analysis established an ee of 92%, the observation of (R)-(−)-**45** in the degradation proved the absolute stereochemistry in (−)-**41b** as S.[59]

Completion of (+)- and (−)-K252a. Having established the sense and degree of asymmetric induction in the preparation of (−)-**41b**, we proceeded with the asymmetric synthesis of **9**. In contrast to **29**, reductive ozonolysis of (−)-**41b** followed by acetal formation provided a ternary mixture. Characterization of the purified products indicated the reaction had produced methyl ketone (−)-**47** in addition to the expected furanoses (+)-**9a** and (+)-**9b** (Scheme 16). The additional component proved to be of no consequence as exposure of **4c** to the ternary mixture [i.e., (+)-**9a,b**, and (−)-**47**] under our standard cycloglycosidation conditions produced the expected regioisomeric mixture of (−)-**33** and (−)-**34** in yields comparable to that observed in the racemic series. Removal of the 3,4-DMB group in (−)-**33** produced (−)-K252a, the enantiomer of the natural product. This observation, in conjunction with the stereochemical assignments made in the course of the degradation study (*vide supra*), allowed the absolute configuration of natural K252a to be established as depicted in (+)-**2** (see Figure 1).

To access (+)-**2** we simply returned to the carbohydrate synthesis and altered the absolute stereochemistry of the starting allylic alcohol. In this series, handling of the allylic alcohol and early intermediates was facilitated by employing the less volatile (R)-(−)-1-nonene-3-ol (**48**) as our initial substrate. Thus, exposure of (R)-(−)-**48** to **36** and catalytic Rh$_2$(OAc)$_4$ (PhH, 80 °C, 20 min) followed by introduction of BF$_3$·OEt$_2$ to the cooled reaction mixture, furnished (+)-**49** in 77% yield (see Scheme 17). Ozonolysis of (+)-**49** followed by acid-mediated cyclization produced the expected carbohydrate mixture [i.e., (−)-**9a,b**/(+)-**47**] in 80% yield.[60] Cycloglycosidation of **4c** with (−)-**9a,b**/(+)-**47** produced (+)-**33** and (+)-**34**, which upon chromatographic separation and deprotection produced (+)-**2**, a compound identical in all respects to the natural material.

Conclusion. The total synthesis of K252a was completed by developing new rhodium carbenoid chemistry in the preparation of **4** and **9**. The total synthesis requires only 12 steps from commercially available materials, with a longest linear sequence of 7 steps and an overall yield of 21% from ethyl glycinate. The remarkable stereo- and regioselective cycloglycosidation
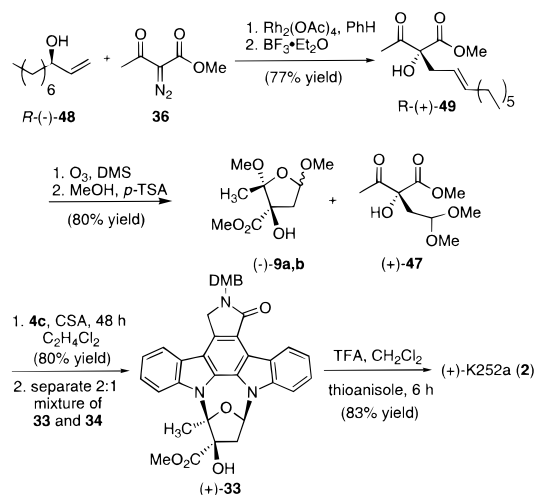
served as the cornerstone of our approach, and the overall efficiency prompted our pursuit of staurosporine (**1**) and other pyranosylated indolocarbazoles.[32]

Experimental Section[61]

Carbazole (16). A mixture of **15** (0.10 g, 0.34 mmol, 1.0 equiv), Pd(PPh$_3$)$_4$ (0.43 g, 0.37 mmol, 1.1 equiv), and Na$_2$CO$_3$ (40 mg, 0.38 mmol, 1.1 equiv) in toluene (1.7 mL) was heated to reflux for 2 h. The reaction mixture was then cooled and evaporated to a residue. Flash chromatography (20:80:1 acetone/hexanes/Et$_3$N eluent) provided **16** (44 mg, 80% yield) as a white solid.[62]

Indolepyrrolidone 19. A mixture of indole (**18**) (1.40 g, 12.0 mmol, 3.0 equiv), diazo lactam **17a** (0.5 g, 4.0 mmol, 1.0 equiv), and Rh$_2$-(OAc)$_4$ (35 mg, 0.08 mmol, 0.02 equiv) in benzene (50 mL) was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to a brown residue which was dissolved in EtOAc (100 mL) and extracted with 1 N NaOH solution (150 mL). The aqueous layer was then acidified to pH 1 with 1 N HCl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H$_2$O (150 mL) and brine solution (150 mL), dried over MgSO$_4$, and concentrated *in vacuo* to provide a crude solid which was recrystallized from EtOAc/heptane to afford **19** (549 mg, 65% yield) as a white powder: mp 220−225 °C (dec); IR (thin film/NaCl) 3405.3 (br m), 2957.0 (m), 2928.3 (s), 2857.7 (m), 1656.6 (s), 1541.3 (w) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 10.23 (br s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.05 (app t, J = 7.8 Hz, 1H), 6.97 (app t, J = 7.4 Hz, 1H), 6.42 (br s, 1H), 4.00 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 174.3, 164.2, 135.6, 126.0, 123.6, 121.8, 120.4, 117.8, 110.8, 106.0, 101.2, 45.0; high-resolution mass spectrum (CI) m/z 215.0805 [calcd for C$_{12}$H$_{11}$N$_2$O$_2$ (M + H) 215.0821].

General Method for the Preparation of Tetramic Acids 25b−e.[63] To a stirred solution of **23** (47.4 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (95 mL) at 0 °C was added a solution of ethyl hydrogen malonate (6.26 g,

(58) Compound **45** has been prepared previously and is of known absolute stereochemistry; see: Spencer, H. K.; Khatri, H. N.; Hill. R. K. *Bioorg. Chem.* **1976**, 5, 177.

(59) This stereochemical outcome suggests a synperiplaner relationship between the hydroxyl and carbonyl oxygens in the reactive conformer. Since BF$_3$·OEt$_2$ is unable to form a chelate its role, if any, in enforcing this transition structure is not obvious.

(60) Upon large-scale preparation of (−)-**9**, a third furanose diastereomer was detected as a minor byproduct. The structure of this compound was unambiguously assigned by X-ray analysis to be the C(2′) epimer of **9a**.[34]

(61) Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and BF$_3$·OEt$_2$ were purchased from the Aldrich Chemical Co. in Sure/Seal containers and used without further purification. All other commercially obtained reagents were used as received. Preparative thin-layer chromatography (TLC) as well as analytical TLC was performed using silica gel 60 F254 precoated plates (0.25 mm). Silica gel (particle size 0.032−0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Melting points are uncorrected. ^{1}H and ^{13}C chemical shifts are reported as δ values relative to tetramethylsilane. High-resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Microanalyses were performed by Atlantic Microlab (Norcross, GA). Single-crystal X-ray analyses were performed by Dr. Susan DeGala of Yale University.

(62) The material obtained proved identical to a sample purchased from Aldrich Chemical Co.

47.4 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (38 mL), followed by a solution of 1,3-dicyclohexylcarbodiimide (9.9 g, 48.0 mmol, 1.01 equiv) and DMAP (290 mg, 2.37 mmol, 0.05 equiv) in CH$_2$Cl$_2$ (20 mL). The mixture was stirred at 0 °C for 15 min and allowed to warm to ambient temperature while being stirred for an additional 2 h. After this time, the solid urea byproduct was removed by filtration. The filtrate was washed with H$_2$O (80 mL), dried over MgSO$_4$, filtered, and evaporated to a yellow semisolid. To this was added acetone (30 mL) and the insoluble precipitate again removed via filtration. The filtrate was concentrated *in vacuo* to a yellow oil and used in the next step without further purification.

To a solution of NaOEt/EtOH prepared from sodium metal (1.09 g, 47.4 mmol) and absolute EtOH (31 mL) was added a solution of the crude diester in benzene (200 mL) over 5 min. The resulting mixture was brought to reflux for 6.5 h. The reaction mixture was allowed to cool to room temperature and then diluted with H$_2$O (100 mL). The layers were separated and the benzene layer further extracted with H$_2$O (2 × 80 mL). The aqueous layers were combined, and residual EtOH was removed *in vacuo*, followed by careful acidification to pH 1 with concentrated HCl at 0 °C. The resultant white precipitate was filtered and dried with a slow stream of N$_2$ gas to give lactams **25b−e** as white powders.

25c. The above procedure was followed using **24c** (12.00 g) to afford **25c** (12.6 g, 83% yield): mp 154−156 °C (EtOH/CH$_2$Cl$_2$); IR (thin film/NaCl) 2937.5 (br m), 2839.5 (w), 2612.4 (br w), 1704.0 (s), 1611.8 (s), 1514.9 (s), 1418.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.89 (d, $J = 8.2$ Hz, 1H), 6.79 (d, $J = 1.6$ Hz, 1H), 6.70 (dd, $J = 1.5$, 8.1 Hz, 1H), 4.37 (s, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.6, 167.3, 162.0, 148.8, 148.0, 130.0, 119.8, 111.9, 111.5, 97.8, 59.0, 55.5, 55.4, 49.0, 44.1, 14.3; high-resolution mass spectrum (EI) m/z 321.1209 [calcd for C$_{16}$H$_{19}$NO$_6$ (M$^+$) 321.1212]. Anal. Calcd for C$_{16}$H$_{19}$NO$_6$: C, 59.81; H, 5.96; N, 4.46. Found: C, 59.93; H, 5.92; N, 4.36.

Diazo Lactams 17b−e. A solution of ester **25** (33.5 mmol, 1.0 equiv) and H$_2$O (1mL) was heated to reflux in CH$_3$CN (1.5 L) for 2 h. The volume of CH$_3$CN was reduced to approximately 35% the original volume (ca. 560 mL) *in vacuo*. The solution was cooled to 0 °C and treated sequentially with MsN$_3$ (8.12 g, 67.0 mmol, 2.0 equiv) in CH$_3$CN (168 mL) via addition funnel followed by Et$_3$N (9.34 mL, 67.0 mmol, 2.0 equiv) in CH$_3$CN (96 mL). After 15 min, the ice bath was removed and the dark orange solution was allowed to warm to 25 °C, stirred for an additional 2 h, and concentrated *in vacuo*. The dark orange residue was dissolved in a minimum of EtOAc and filtered through a pad of silica gel (EtOAc eluent). The filtrate was washed once with 1 N NaOH solution, dried over MgSO$_4$, filtered, and concentrated to give **17b−e** as yellow solids, which were recrystallized from acetone/hexanes.

17c. The above procedure was followed using **25c** (10.75 g) to afford **17c** (8.29 g, 90% yield): mp 145−147 °C (EtOAc); IR (CCl$_4$) 2960.7 (br w), 2925.8 (br w), 2126.1 (s), 1695.2 (s), 1515.1 (m), 1451.2 (w), 1401.1 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.83 (d, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 8.6$ Hz, 1H), 6.79 (s, 1H), 4.53 (s, 2H), 3.88 (s, 6H), 3.71 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.7, 161.7, 149.5, 149.0, 127.7, 120.8, 111.3, 111.2, 66.0, 56.0, 55.9, 53.9, 46.5; high-resolution mass spectrum (CI) m/z 276.0981 [calcd for C$_{13}$H$_{14}$N$_3$O$_4$ (M + H) 276.0984]. Anal. Calcd for C$_{13}$H$_{13}$N$_3$O$_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.81; H, 4.81; N, 15.36.

Indolocarbazoles 4a−e. Method A.[63] A mixture of 2,2′-biindole (**20**) (200 mg, 0.86 mmol, 1.0 equiv), diazotetramic acid **17a−e** (2.2 mmol, 2.5 equiv), Rh$_2$(OAc)$_4$ (38 mg, 0.086 mmol, 0.1 equiv), and pinacolone (8.6 mL) in a pressure tube fitted with a rubber septum was degassed with a stream of N$_2$ for 1 h. The septum was removed and the tube was flushed with N$_2$, sealed, and placed into a preheated sand bath (120 °C). After 6 h, the tube was removed from the sand bath, allowed to cool to room temperature, and carefully opened. After removing the solvent *in vacuo*, the residue was dissolved in EtOAc (15 mL), washed with 1 N NaOH (15 mL) solution, and dried over MgSO$_4$. Filtration and removal of the solvent was followed by flash

chromatography (1:1 EtOAc/hexanes eluent) to provide **4a−e** as pale yellow solids.

4c. The above procedure was followed using **17c** (605 mg) to afford **4c** (257 mg, 62% yield): mp >202 °C (dec, EtOAc); IR (thin film/NaCl) 3487.5 (br s), 3352.0 (br s), 3232.0 (br s), 3022.3 (m), 1579.1 (s), 1571.2 (s), 1517.7 (s), 1462.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 11.35 (br s, 1H), 9.28 (d, $J = 7.9$ Hz, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 8.1$ Hz, 1H), 7.45 (app t, $J = 6.9$ Hz, 1H), 7.44 (app t, $J = 7.1$ Hz, 1H), 7.26 (app t, $J = 7.1$ Hz, 1H), 7.25 (app t, $J = 7.1$ Hz, 1H), 7.02 (s, 1H), 6.92 (s, 2H), 4.94 (s, 2H), 4.82 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 169.2, 148.9, 148.1, 139.1, 139.0, 130.6, 130.0, 127.7, 125.3, 124.9, 124.9, 124.8, 122.6, 122.3, 120.7, 119.9, 119.7, 118.8, 118.2, 115.4, 113.8, 112.3, 112.1, 111.7, 111.1, 55.5, 49.3, 45.4; high-resolution mass spectrum (FAB) m/z 462.1813 [calcd for C$_{29}$H$_{24}$N$_3$O$_3$ (M + H) 462.1818].

Indolocarbazole 4c and Isolation of 26. Method B. A mixture of **20** (4.0 g, 17.2 mmol, 1.0 equiv), lactam **17c** (4.74 g, 17.2 mmol, 1.0 equiv), Rh$_2$(OAc)$_4$ (76 mg, 0.17 mmol, 0.01 equiv), and pinacolone (210 mL), in a three-neck round-bottom flask fitted with a reflux condenser was degassed with a stream of N$_2$ for 2 h. The reaction mixture was then heated to reflux for 8 h. The mixture was allowed to cool to room temperature, and the solvent was evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) afforded unreacted **20** (2.0 g, 50% yield) as a pale yellow powder and **4c** (2.9 g, 36% yield; 72% yield based on recovered **20**) as a white solid.

When heating was discontinued after only 3 h and the reaction mixture worked up in the fashion described above, **20** (1.92 g) and **4c** (1.15 g) were isolated, along with **26** (644 mg) as a yellow foam: IR (thin film/NaCl) 3323.5 (br m), 2935.8 (w), 2829.1 (w), 1676.6 (s), 1514.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 10.87 (br s, 1H), 8.27 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 8.1$ Hz, 1H), 7.16 (td, $J = 1.0$, 7.4 Hz, 1H), 7.03−7.12 (comp m, 3H), 6.87 (s, 1H), 6.69 (s, 2H), 6.65 (s, 1H), 6.58 (s, 1H), 4.59 (d, $J = 14.9$ Hz, 1H), 4.43 (s, 1H), 4.32 (d, $J = 14.8$ Hz, 1H), 3.97 (d, $J = 10.1$ Hz, 1H), 3.65 (s, 3H), 3.39 (d, $J = 10.2$ Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.3, 150.0, 149.1, 138.6, 137.2, 130.5, 129.2, 127.2, 127.1, 123.3, 122.6, 121.9, 121.0, 121.0, 120.4, 120.3, 113.6, 112.0, 111.5, 111.4, 110.9, 103.8, 97.5, 87.6, 57.8, 55.5, 54.9, 53.2, 45.5; high-resolution mass spectrum (EI) m/z 479.1845 [calcd for C$_{29}$H$_{25}$N$_3$O$_4$ (M$^+$) 479.1845].

Acetoacetate 29. A suspension of sodium hydride (5.55 g, 60% dispersion in mineral oil, 139 mmol, 1.01 equiv) in dioxane (135 mL) was treated dropwise with a solution of methyl 2-(methylcarbonyloxy)-3-oxobutanoate[33] (24.1 g, 138 mmol, 1.0 equiv) in dioxane (27 mL) over a period of 45 min. The mixture was stirred (overhead stirrer) for an additional 45 min at 20 °C. Prenyl bromide (15.95 mL, 138 mmol, 1.0 equiv) was added over 25 min, and the mixture warmed to reflux for 20 min. After cooling to room temperature, the mixture was poured into 1.1 L of H$_2$O containing acetic acid (7.9 mL, 138 mmol, 1.0 equiv). This mixture was extracted with ether (1 × 600 mL; 3 × 300 mL). The organic layer was washed with H$_2$O (500 mL) and saturated NaCl solution (500 mL) and dried over MgSO$_4$. The solvent was evaporated and the reaction mixture distilled (bp 80−85 °C, 0.2 mmHg) to provide **29** as a colorless oil (28.53 g, 85% yield): IR (thin film/NaCl) 2997.1 (w), 2955.7 (m), 2929.3 (m), 2917.9 (m), 2859.7 (w), 1747.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.99 (t, $J = 7.4$ Hz, 1H), 3.75 (s, 3H), 2.88 (app t, $J = 6.3$ Hz, 2H), 2.32 (s, 3H), 2.17 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.5, 169.3, 167.5, 136.7, 115.2, 87.3, 52.5, 32.5, 26.6, 25.6, 20.3, 17.5; high-resolution mass spectrum (CI) m/z 243.1233 [calcd for C$_{12}$H$_{19}$O$_5$ (M + H) 243.1232].

Acetates (±)-30a,b. A solution of **29** (2.91 g, 12.0 mmol, 1.0 equiv) and a trace of sudan red 7B dye in a mixture of THF (65 mL) and MeOH (13 mL) was cooled to −78 °C and treated with O$_3$ until the dye was completely discolored (about 6 min). The mixture was purged with argon for 10 min at −78 °C, and dimethyl sulfide (40 mL) was added at that temperature. The reaction was brought to 0 °C with an ice bath which was allowed to thaw (0−20 °C) over a period of 3 h. The solvent was removed and the crude product dissoved in MeOH (20 mL). After addition of trimethyl orthoformate (6.6 mL, 60.0 mmol, 5.0 equiv) and *p*-toluenesulfonic acid (22.8 mg, 0.12 mmol, 0.01 equiv),

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(63) Due to space limitations, spectral data pertaining to the **b**, **d**, and **e** analogs are provided as Supporting Information.

the mixture was heated to reflux for 1 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) provided a mixture of diastereomers **30a,b** (2.36 g, 75% yield) as a colorless oil. The diastereomers could be separated using HPLC (4:4:1 hexanes/CH$_2$Cl$_2$/EtOAc eluent). Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/hexanes.

30a: mp 106–107 °C; IR (thin film/NaCl) 2996.6 (w), 2953.1 (m), 2917.3 (m), 2837.2 (w), 1759.8 (s), 1741.3 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.11 (app t, J = 5.7 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 3.27 (s, 3H), 3.15 (dd, J = 5.3, 15.3 Hz, 1H), 2.57 (dd, J = 6.2, 15.3 Hz, 1H), 2.10 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.5, 167.3, 108.8, 104.9, 88.4, 56.4, 52.5, 48.6, 39.2, 20.8, 15.0; high-resolution mass spectrum (CI) *m/z* 231.0866 [calcd for C$_{10}$H$_{15}$O$_6$ (M − CH$_3$OH + H) 231.0869].

30b: mp 58–59 °C; IR (thin film/NaCl) 2998.2 (m), 2952.9 (s), 2977.7 (m), 2838.7 (m), 1760.0 (s), 1739.9 (s), 1434.2 (s), 1376.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.08 (dd, J = 1.9, 6.5 Hz, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 3.33 (dd, J = 6.5, 15.2 Hz, 1H), 3.25 (s, 3H), 2.19 (dd, J = 1.9, 15.2 Hz, 1H), 2.11 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.7, 167.7, 109.0, 104.1, 86.4, 55.9, 52.5, 48.6, 39.1, 20.9, 15.8; high-resolution mass spectrum (CI) *m/z* 231.0870 [calcd for C$_{10}$H$_{15}$O$_6$ (M − CH$_3$OH + H) 231.0869].

Esters (±)-9a,b. A solution of **30a,b** (1.31 g, 5.00 mmol) in MeOH (50 mL) was treated with K$_2$CO$_3$ (1.04 g, 7.52 mmol, 1.5 equiv). The mixture was stirred for 2 h at 20 °C. After evaporation of solvent *in vacuo*, the residue was dissolved in Et$_2$O and filtered through silica gel (Et$_2$O eluent) to afford a mixture of (±)-**9a,b** (814 mg, 74% yield) as a colorless oil. The mixture of diastereomers could be separated by HPLC (2:2:1 hexanes/CH$_2$Cl$_2$/EtOAc eluent).

Indolocarbazoles (±)-33 and (±)-34. A stirred solution of aglycon **4c** (1.00 g, 2.17 mmol, 1.0 equiv) and camphorsulfonic acid (50 mg, 0.22 mmol, 0.1 equiv) in 1,2-dichloroethane (72 mL) was heated to reflux and treated over 24 h with a solution of (±)-**9a,b** (0.95 g, 4.32 mmol, 2.0 equiv) in 1,2-dichloroethane (50 mL). After an additional 24 h, the reaction mixture was allowed to cool to room temperature, diluted with CH$_2$Cl$_2$ (50 mL), and washed with 10% NaHCO$_3$ solution (50 mL). The organic layer was dried with Na$_2$SO$_4$ and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) provided a 2:1 mixture of (±)-**33** and (±)-**34** (1.07 g, 80% yield). Separation of the regioisomers (±)-**33** and (±)-**34** was achieved with either preparative TLC (60:1 70% CH$_2$Cl$_2$/hexanes/MeOH, three elutions) or by HPLC (190:10:1 CH$_2$Cl$_2$/EtOAc/MeOH eluent).

Ketone (±)-35. To a solution of (±)-**9a,b** (230 mg, 1.00 mmol, 1.0 equiv) and carbazole (**16**) (167 mg, 1.00 mmol, 1.0 equiv) in 10 mL of 1,2-dichloroethane was added camphorsulfonic acid (23.0 mg, 0.10 mmol, 0.10 equiv), and the mixture was heated to reflux for 10 h. Removal of solvent followed by flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture (1:1) of diastereomeric ketones (±)-**35** (274 mg, 77% yield). The first compound to elute was diastereomer **I**: IR (thin film/NaCl) 3451.2 (m), 3057.5 (w), 3046.5 (w), 2997.5 (w), 2950.2 (m), 2828.5 (w), 1746.5 (s), 1722.2 (s), 1627.3 (w), 1600.2 (m), 1483.6 (s), 1453.7 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, J = 7.7 Hz, 2H), 7.43 (t, J = 7.4 Hz, 4H), 7.24 (t, J = 7.5 Hz, 2H), 5.92 (dd, J = 4.4, 8.8 Hz, 1H), 4.68 (s, 1H), 3.40 (s, 3H), 3.25 (dd, J = 8.8, 14.8 Hz, 1H), 3.12 (s, 3H), 2.64 (dd, J = 4.4, 14.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.7, 170.1, 139.1, 125.8, 123.7, 120.2, 119.8, 110.5, 83.4, 81.9, 55.7, 53.0, 38.7, 24.5; high-resolution mass spectrum (FAB) *m/z* 355.1411 [calcd for C$_{20}$H$_{21}$NO$_5$ (M$^+$) 355.1420].

The second compound to elute was diastereomer **II**: IR (thin film/NaCl) 3466.3 (w), 3058.7 (w), 2996.6 (w), 2950.7 (w), 2930.0 (w), 2847.2 (w), 2828.3 (w), 1723.7 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.4 Hz, 4H), 7.25 (t, J = 7.3 Hz, 2H), 5.97 (dd, J = 4.1, 9.1 Hz, 1H), 4.54 (s, 1H), 3.89 (s, 3H), 3.36 (dd, J = 9.1, 14.5 Hz, 1H), 3.17 (s, 3H), 2.33 (dd, J = 4.1, 14.5 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.4, 171.4, 139.6, 125.9, 123.7, 120.3, 119.8, 110.6, 83.5, 81.8, 56.1, 53.5, 38.7, 24.2; high-resolution mass spectrum (FAB) *m/z* 355.1411 [calcd for C$_{20}$H$_{21}$NO$_5$ (M$^+$) 355.1420].

Ketones (±)-31 and (±)-32. A stirred solution of aglycon **4c** (250 mg, 0.54 mmol, 1.0 equiv) and camphorsulfonic acid (12.5 mg, 0.054

mmol, 0.1 equiv) was heated to reflux in 1,2-dichloroethane (18 mL) and treated over 30 min with a solution of (±)-**14a**, **b** (0.24 g, 1.1 mmol, 2.0 equiv) in dichloroethane (12 mL). After an additional 45 min at reflux, the reaction mixture was allowed to cool to room temperature, diluted with CH$_2$Cl$_2$ (25 mL), and washed with 10% NaHCO$_3$ solution (20 mL). The organic layer was dried with Na$_2$SO$_4$ and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) provided a 2:1 mixture of (±)-**31** and (±)-**32** (260 mg, 74% yield). Separation of the regioisomers (±)-**31** and (±)-**32** was achieved using either preparative TLC (1:20:20 MeOH/CH$_2$Cl$_2$/hexanes, 3 elutions) or HPLC (190:10:1 CH$_2$Cl$_2$/EtOAc/MeOH eluent).

The first diastereomeric mixture to elute was minor regioisomer (±)-**32**: IR (thin film/NaCl) 3388.2 (br m), 2928.3 (s), 1731.6 (s), 1668.6 (s), 1592.9 (m), 1514.7 (m), 1454.4 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.08 (br s, 1H), 9.98 (br s, 1H), 9.58 (app t, J = 8.0 Hz, 2H), 7.89 (d, J = 7.7 Hz, 2H), 7.70 (d, J = 4.7 Hz, 1H), 7.68 (d, J = 4.8 Hz, 1H), 7.50–7.62 (comp m, 6H), 7.41 (app t, J = 7.6 Hz, 2H), 7.35 (app t, J = 7.4 Hz, 2H), 6.99 (m, 4H), 6.89 (s, 1H), 6.87 (s, 1H), 6.28 (dd, J = 3.8, 9.8 Hz, 1H), 6.22 (dd, J = 4.6, 8.9 Hz, 1H), 4.97 (s, 4H), 4.90 (app t, J = 17.1 Hz, 4H), 4.59 (s, 1H), 4.50 (s, 1H), 4.07 (s, 3H), 3.89 (s, 6H), 3.86 (s, 6H), 3.49 (dd, J = 9.9, 14.5 Hz, 1H), 3.45 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.33 (dd, J = 8.9, 14.8 Hz, 1H), 2.45 (s, 3H), 2.42 (dd, J = 4.5, 14.8 Hz, 1H), 2.13 (dd, J = 4.0, 14.6 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.4, 202.9, 171.5, 170.2, 170.0, 149.4, 148.5, 139.9, 139.6, 139.5, 139.5, 130.4, 129.6, 129.6, 126.8, 126.7, 126.4, 126.4, 126.0, 125.9, 125.7, 125.6, 125.4, 123.3, 123.3, 123.2, 121.3, 121.2, 121.1, 120.8, 120.4, 120.2, 120.1, 118.4, 118.4, 116.3, 116.3, 111.2, 111.2, 110.9, 110.7, 110.6, 109.5, 109.3, 83.6, 83.6, 82.0, 81.8, 56.8, 56.6, 56.0, 55.9, 53.9, 53.6, 49.6, 46.4, 40.5, 24.9, 23.9; high-resolution mass spectrum (EI) *m/z* 649.2422 [calcd for C$_{37}$H$_{35}$N$_3$O$_8$ (M$^+$) 649.2424].

The second diastereomeric mixture to elute was major regioisomer (±)-**31**: IR (thin film/NaCl) 3381.1 (br m), 3009.5 (w), 2942.3 (m), 2841.8 (w), 1725.6 (s), 1668.7 (s), 1513.6 (s), 1454.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.25 (br s, 1H), 10.15 (br s, 1H), 9.68 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 3.8 Hz, 1H), 7.92 (d, J = 3.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.51–7.58 (comp m, 4H), 7.41 (app t, J = 7.7 Hz, 2H), 7.34 (app t, J = 7.3 Hz, 2H), 6.99 (m, 4H), 6.87 (d, J = 8.1 Hz, 2H), 6.30 (dd, J = 3.8, 10.0 Hz, 1H), 6.26 (dd, J = 4.6, 8.9 Hz, 1H), 4.98 (d, J = 14.9 Hz, 1H), 4.98 (d, J = 14.9 Hz, 1H), 4.93 (d, J = 15.0 Hz, 1H), 4.92 (d, J = 15.0 Hz, 1H), 4.89 (s, 4H), 4.61 (s, 1H), 4.51 (s, 1H), 4.06 (s, 3H), 3.89 (s, 6H), 3.89 (s, 6H), 3.47 (s, 3H), 3.46 (s, 3H), 3.43–3.45 (m, 1H), 3.41 (s, 3H), 3.28 (dd, J = 9.0, 14.8 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, J = 4.7, 14.7 Hz, 1H), 2.12 (s, 3H), 2.09 (dd, J = 3.8, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.0, 203.0, 171.7, 170.4, 170.1, 149.3, 148.5, 139.7, 139.5, 139.4, 139.4, 131.5, 130.4, 127.9, 127.7, 126.8, 126.8, 126.2, 125.9, 125.9, 125.6, 125.5, 125.0, 124.6, 124.4, 123.8, 123.7, 122.8, 122.8, 121.0, 121.0, 120.8, 120.7, 120.4, 120.4, 119.2, 119.1, 115.7, 115.7, 111.8, 111.6, 111.2, 111.1, 110.9, 108.5, 108.3, 107.3, 83.4, 83.4, 82.1, 81.9, 56.7, 56.4, 56.0, 55.9, 53.7, 53.7, 49.5, 46.4, 40.4, 40.4, 25.0, 23.9; high-resolution mass spectrum (EI) *m/z* 649.2415 [calcd for C$_{37}$H$_{35}$N$_3$O$_8$ (M$^+$) 649.2424].

(±)-K252a (2). To a stirred solution of (±)-**33** (17.0 mg, 0.028 mmol, 1 equiv) in CH$_2$Cl$_2$ (1.4 mL) at 25 °C was added thioanisole (0.16 mL, 1.36 mmol, 50 equiv) followed by 2,2,2-trifluoroacetic acid (1.4 mL). The solution was stirred for 6 h, followed by dropwise addition of 2.0 mL of saturated NaHCO$_3$ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH/CH$_2$Cl$_2$/hexanes, three elutions) to afford (±)-K252a [**2**, 10.8 mg, 83% yield].

Ketone (+)-40. A stirred solution of methyl 2-diazo-3-oxobutanoate (**33**) (2.13 g, 15.0 mmol, 1.0 equiv), (S)-(+)-**38** (1.3 mL, 15.0 mmol, 1.0 equiv), and Rh$_2$(OAc)$_4$ (66.3 mg, 0.15 mmol, 0.01 equiv) in benzene (75 mL) was immersed into a preheated (100–110 °C) oil bath. The mixture was heated under reflux for 20 min. After the mixture was cooled to room temperature, the solvent was carefully evaporated (0 °C) *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) afforded (+)-**40** (1.84 g, 66% yield) as a colorless oil: bp 65–67 °C (0.35 mmHg); [α]$^{20}_D$ +14.65 (*c* 1.08, CHCl$_3$); IR (thin film/NaCl) 3521.0 (m), 3028.5 (w), 2981.5 (m), 2957.1 (m), 2937.9 (m), 2919.9 (m), 2857.4 (w), 1742.6 (s), 1726.1 (s) cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$) δ 5.57 (m, 1H), 5.35 (m, 1H), 3.88 (s, 3H), 3.28 (br s, 1H), 2.68 (dd, J = 7.0, 14.0 Hz, 1H), 2.42 (dd, J = 7.7, 14.0 Hz, 1H), 1.66 (d, J = 6.42 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.5, 162.7, 130.9, 123.5, 78.3, 52.5, 42.2, 24.1, 17.8; high-resolution mass spectrum (CI) *m/z* 187.0966 [calcd for C$_9$H$_{15}$O$_4$ (M + H) 187.0970].

Ketone (−)-41b. A solution of (+)-**40** (3.35 g, 18.0 mmol, 1.0 equiv) in benzene (180 mL) was treated with BF$_3$·OEt$_2$ (2.21 mL, 18.0 mmol, 1.0 equiv), stirred for 2 h at 25 °C, and the solvent was carefully evaporated (0 °C) *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) provided (−)-**41b** (2.49 g, 74% yield) as a colorless oil: [α]$^{20}_D$ −32.13 (*c* 1.08, CHCl$_3$); IR (thin film/NaCl) 3476.1 (m), 3031.2 (w), 3009.6 (w), 2956.2 (m), 2921.4 (w), 2857.5 (w), 1746.9 (s), 1721.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.60 (m, 1H), 5.32 (m, 1H), 4.17 (s, 1H), 3.80 (s, 3H), 2.77 (dd, J = 6.6, 14.3 Hz, 1H), 2.63 (dd, J = 7.6, 14.3 Hz, 1H), 2.28 (s, 3H), 1.65 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.2, 170.8, 130.5, 122.9, 83.8, 53.1, 38.5, 24.7, 17.9; high-resolution mass spectrum (CI) *m/z* 187.0969 [calcd for C$_9$H$_{15}$O$_4$ (M + H) 187.0970].

Ketone (−)-41b. Single-Pot Method. A stirred solution of methyl 2-diazo-3-oxobutanoate (**36**) (427 mg, 3.00 mmol, 1.0 equiv), (S)-(+)-**38** (0.286 mL, 3.3 mmol, 1.1 equiv), and Rh$_2$(OAc)$_4$ (13 mg, 0.03 mmol, 0.01 equiv) in benzene (15 mL) was immersed into a preheated (100−110 °C) oil bath. The mixture was heated to reflux for 20 min, cooled to room temperature, treated with BF$_3$·OEt$_2$ (0.46 mL, 3.74 mmol, 1.25 equiv), and stirred for 2 h at 25 °C. The entire reaction mixture was poured onto a silica column and chromatographed (20% pentane/Et$_2$O eluent) to provide (−)-**41b** (418 mg, 75% yield) as a colorless oil.

Esters (+)-9a,b and Ketone (−)-47. A solution of (−)-**41b** (1.31 g, 7.0 mmol, 1.0 equiv) and a trace of sudan red 7B dye in MeOH (45 mL) was cooled to −78 °C and treated with O$_3$ until the dye was completely discolored (about 3 min). The mixture was purged with argon for 10 min at −78 °C, and dimethyl sulfide (20 mL) was added at that temperature. The dry ice bath was replaced with an ice bath which was allowed to thaw (0−20 °C) over a period of 3 h. The solvent was removed *in vacuo* and the crude product dissoved in benzene (45 mL). After addition of *p*-toluenesulfonic acid (20 mg, 0.11 mmol, 0.015 equiv) and MeOH (12 mL) the mixture was stirred at 25 °C for 17 h followed by evaporation of the solvent *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture of diastereomers (+)-**9a,b** and (−)-**47** (1.23 g, 80% yield). The diastereomers could be separated using HPLC. In a first run (2:2:1 hexanes/CH$_2$Cl$_2$/EtOAc eluent), a mixture of (+)-**9b** and (−)-**47** was eluted first followed by (+)-**9a** which was isolated in its pure form as a colorless oil. The two-component mixture was separated using a different system (10% 2-propanol/hexanes eluent). The first compound to elute was furanose (+)-**9b**, followed by ketone (−)-**47**, both as colorless oils.

Indolocarbazoles (−)-33 and (−)-34. A procedure identical to that described for the preparation of (±)-**33** and (±)-**34** was employed, with the exception that the mixture of (+)-**9a,b** and (−)-**47** obtained above was utilized in place of the racemic carbohydrate substrate: (−)-**33**, [α]$^{20}_D$ −17 (*c* 0.1, MeOH). (−)-**34**, [α]$^{20}_D$ −13 (*c* 0.1, MeOH).

(−)-K252a (2). A procedure identical to that for the preparation of (±)-**2** was employed to provide (−)-**2** ([α]$^{20}_D$ −39; *c* 0.1, MeOH) from (−)-**33**.

Ketone (+)-49. A stirred solution of methyl 2-diazo-3-oxobutanoate (**36**) (10 g, 70.4 mmol, 1.0 equiv), (R)-(−)-nonen-3-ol (10.8 g, 75.9 mmol, 1.1 equiv), and Rh$_2$(OAc)$_4$ (19 mg, 0.04 mmol, 0.0006 equiv) in benzene (235 mL) was immersed into a preheated (100−110 °C) oil bath. The mixture was heated at reflux for 20 min, cooled to room temperature, treated with BF$_3$·OEt$_2$ (10.8 mL, 85.2 mmol, 1.21 equiv), and stirred for 2 h at 25 °C. The entire reaction mixture was poured onto a flash column and chromatographed (10% EtOAc/hexanes eluent) to provide (+)-**49** (13.9 g, 77% yield) as a colorless oil: [α]$^{20}_D$ +19.41 (*c* 1.03, CHCl$_3$); IR (thin film/NaCl) 3788.3 (m), 2954.9 (s), 2926.7 (s), 2871.3 (m), 2855.5 (s), 1746.6 (s), 1723.2 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.57 (m, 1H), 5.30 (m, 1H), 4.20 (s, 1H), 3.79 (s, 3H), 2.78 (dd, J = 6.7, 14.3 Hz, 1H), 2.64 (dd, J = 7.6, 14.3 Hz, 1H), 2.28 (s, 3H), 1.97 (q, J = 7 Hz, 2H), 1.31−1.23 (m, 8H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.2, 170.8, 136.2, 121.6, 83.9, 53.1, 38.6, 32.4, 31.5, 29.0, 28.6, 24.7, 22.4, 13.9; high-resolution mass spectrum (CI) *m/z* 257.1745 [calcd for C$_{14}$H$_{25}$O$_4$ (M + H) 257.1753].

Esters (−)-9a,b and Ketone (+)-47. The same procedure used for the preparation of (+)-**9a,b** and (−)-**47** was employed. Ketone (+)-**49** (10.6 g, 41.4 mmol) was used as starting material yielding the three-component mixture (1:1:1), (−)-**9a,b** and (+)-**47** (7.3 g, 80% yield). Separation of the mixture was achieved using the same protocol described above.

(−)-9b: mp 63−64 °C (EtOAc); [α]$^{20}_D$ −9.00 (*c* 1.16, CHCl$_3$); IR (thin film/NaCl) 3486.7 (m), 2994.8 (m), 2954.8 (m), 2918.0 (m), 2836.2 (m), 1732.7 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.21 (app t, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.36 (br s, 1H), 3.27 (s, 3H), 2.84 (dd, J = 5.3, 14.3 Hz, 1H), 2.34 (dd, J = 6.2, 14.3 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.1, 109.9, 105.4, 84.5, 56.4, 52.8, 49.0, 40.5, 14.5; high-resolution mass spectrum (CI) *m/z* 189.0773 [calcd for C$_8$H$_{13}$O$_5$ (M − CH$_3$OH + H) 189.0763].

(−)-9a: mp 81−82 °C (EtOAc); [α]$^{20}_D$ −122.55 (*c* 1.10, CHCl$_3$); IR (thin film/NaCl) 3496.4 (m), 2998.9 (m), 2953.3 (m), 2915.1 (m), 2836.9 (m), 1748.9 (s), 1732.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.07 (d, J = 5.8 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 3.25 (s, 3H), 3.03 (dd, J = 5.8, 14.1 Hz, 1H), 2.05 (d, J = 14.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.4, 110.5, 103.8, 83.1, 55.5, 52.5, 49.2, 40.5, 15.7; high-resolution mass spectrum (CI) *m/z* 189.0778 [calcd for C$_8$H$_{13}$O$_5$ (M − CH$_3$OH + H) 189.0763].

(+)-47: [α]$^{20}_D$ +19.55 (*c* 1.12, CHCl$_3$); IR (thin film/NaCl) 3452.5 (m), 2993.2 (m), 2954.6 (m), 2934.2 (m), 2917.5 (m), 2848.4 (m), 2838.2 (m), 1748.7 (s), 1723.1 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.51 (br s, 1H), 4.50 (dd, J = 4.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.43 (dd, J = 4.9, 14.6 Hz, 1H), 2.38 (dd, J = 6.6, 14.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.0, 170.8, 102.0, 81.8, 54.9, 53.8, 53.2, 38.4, 24.5; high-resolution mass spectrum (FAB) *m/z* 189.0775 [calcd for C$_8$H$_{13}$O$_5$ (M − CH$_3$OH + H) 189.0763].

Indolocarbazoles (+)-33 and (+)-34. A procedure identical to that described for the preparation of (±)-**33** and (±)-**34** was employed, with the exception that the mixture of (−)-**9a,b** and (+)-**47** obtained above was utilized in place of the racemic carbohydrate substrate.

(+)-33: mp >250 °C (dec, MeOH/CH$_2$Cl$_2$); [α]$^{20}_D$ +15 (*c* 0.1, MeOH); IR (thin film/NaCl) 3279.7 (br m), 3012.1 (m), 2952.1 (m), 2930.1 (m), 2850.1 (w), 1732.2 (m), 1646.2 (s), 1590.4 (m), 1513.7 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.26 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.92 (app t, J = 8.0 Hz, 2H), 7.49 (app t, J = 7.7 Hz, 1H), 7.47 (app t, J = 7.8 Hz, 1H), 7.32 (app t, J = 7.9 Hz, 1H), 7.30 (app t, J = 8.1 Hz, 1H), 7.15 (dd, J = 5.2, 6.9 Hz, 1H), 7.02 (s, 1H), 6.94 (d, J = 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.35 (s, 1H), 5.02 (d, J = 17.8 Hz, 1H), 4.97 (d, J = 17.8 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (dd, J = 7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, J = 4.7, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-*d$_6$*) δ 172.6, 168.6, 148.9, 148.2, 139.8, 136.7, 130.4, 130.0, 128.2, 125.3, 125.3, 124.8, 123.9, 123.8, 122.4, 120.9, 120.2, 119.8, 119.3, 118.9, 115.6, 114.6, 114.2, 112.3, 112.1, 108.8, 99.3, 84.8, 55.5, 52.4, 49.5, 45.4, 42.4, 22.6; high-resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for C$_{36}$H$_{32}$N$_3$O$_7$ (M + H) 618.2240].

(+)-34: mp 260−270 °C (dec, MeOH/CH$_2$Cl$_2$); [α]$^{20}_D$ +13 (*c* 0.1, MeOH); IR (thin film/NaCl) 3462.3 (br m), 3014.0 (m), 2952.3 (m), 2925.1 (m), 2849.7 (m), 1730.8 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.54 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.50 (app t, J = 7.5 Hz, 1H), 7.45 (app t, J = 7.5 Hz, 1H), 7.30 (app t, J = 7.5 Hz, 1H), 7.29 (app t, J = 7.6 Hz, 1H), 7.14 (dd, J = 5.0, 7.2 Hz, 1H), 7.01 (s, 1H), 6.92 (app t, J = 8.2 Hz, 1H), 6.92 (dd, J = 1.1, 8.4 Hz, 1H), 6.34 (br s, 1H), 4.98 (d, J = 17.9 Hz, 1H), 4.95 (d, J = 17.9 Hz, 1H), 4.84 (d, J = 15.1 Hz, 1H), 4.80 (d, J = 15.1 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.40 (dd, J = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.05 (dd, J = 4.8, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-*d$_6$*) δ 172.6, 168.9, 149.0, 148.2, 139.7, 136.8, 130.4, 126.2, 126.1, 125.4, 125.1, 124.9, 124.3, 122.0, 121.3, 120.2, 119.8, 119.2, 118.7, 116.3, 113.9, 113.8, 112.3, 112.1, 109.4, 99.3, 84.9, 84.8, 55.5, 52.4, 49.0, 45.4, 42.5, 22.8; high-resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for C$_{36}$H$_{32}$N$_3$O$_7$ (M + H) 618.2240].

(+)-K252a (2). A procedure identical to that for the preparation of (±)-**2** was employed to provide (+)-**2** from (+)-**33**: mp 264−267 °C (dec, acetone); [α]$^{20}_D$ +40 (*c* 0.1, MeOH); IR (thin film/NaCl) 3309.6

(br m), 3053.5 (m), 2952.6 (m), 2851.9 (m), 1735.8 (s), 1675.4 (s), 1590.0 (m), 1458.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (d, $J = 7.9$ Hz, 1H), 8.63 (s, 1H), 8.05 (d, $J = 7.7$ Hz, 1H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.47 (comp m, 2H), 7.35 (app t, $J = 7.4$ Hz, 1H), 7.28 (app t, $J = 7.4$ Hz, 1H), 7.14 (dd, $J = 5.0, 7.2$ Hz, 1H), 6.34 (s, 1H), 5.02 (d, $J = 17.6$ Hz, 1H), 4.97 (d, $J = 17.6$ Hz, 1H), 3.92 (s, 3H), 3.38 (dd, $J = 7.5, 14.0$ Hz, 1H), 2.14 (s, 3H), 2.01 (dd, $J = 4.9, 14.0$ Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 171.8, 139.9, 136.8, 133.0, 128.3, 125.6, 125.4, 125.1, 124.2, 123.9, 122.6, 121.3, 120.4, 119.6, 119.5, 115.8, 114.8, 114.6, 109.1, 99.4, 85.0, 85.0, 52.7, 45.5, 42.5, 22.8; high-resolution mass spectrum (FAB) m/z 468.1561 [calcd for $C_{27}H_{22}N_3O_5$ (M + H) 468.1559].

Supporting Information Available: Spectral and experimental data pertaining to **25b,d,e**; **17b,d,e**; **4a,b,d,e**; **42**; **44**; and **45**. Crystallographic information pertaining to **30a**, **30b**, and C(2′)-epi-**9a** (21 pages). See any current masthead page for ordering and Internet access instructions.

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