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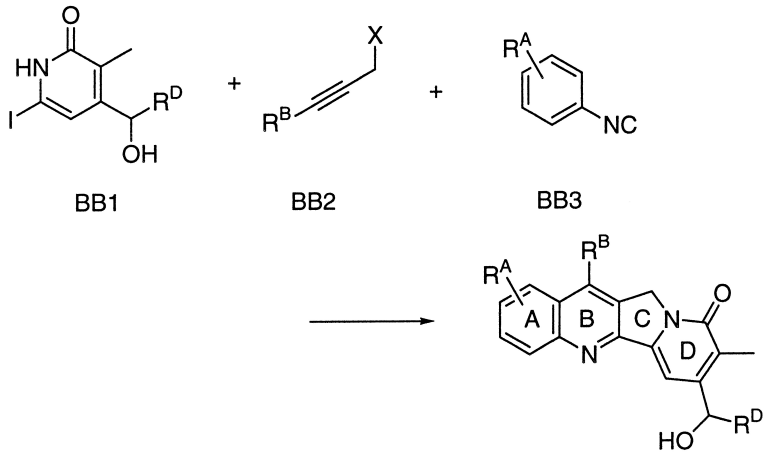

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Solution Phase Synthesis of Libraries of Polycyclic Natural Product Analogues by Cascade Radical Annulation: Synthesis of a 64-Member Library of Mappicine Analogues and a 48-Member Library of Mappicine Ketone Analogues

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An improved cascade radical annulation route to (±)-mappicine, (*S*)-mappicine, and mappicine ketone is reported. The route is used to prepare libraries of mappicine and mappicine ketone analogues in a semiautomated fashion. Key diversity generating steps include the addition of an aldehyde to a Grignard reagent derived from a D-ring iodopyridine, *N*-propargylation of a subsequently derived iodopyridone, and cascade radical annulation with an isonitrile to form a mappicine analogue. Parallel oxidation of mappicine analogues produced mappicine ketones. The route is general and flexible and could be used to make very large libraries. It is also illustrative of how late stage cascade reactions can be employed strategically to generate libraries of polycyclic natural product analogues.

Introduction

The synthesis of combinatorial libraries, either on the solid phase or in solution, has quickly become an indispensable tool in the discovery of new organic molecules with useful functions (drug candidates, ligands, catalysts, etc).[1] Combinatorial libraries are constructed from three or more components in several ways. Multicomponent reactions bring together the components in a single step,[2] while stepwise building of libraries can occur either in a linear fashion or through the attachment of side chains to a core. The majority of libraries built to date either introduce no new rings at all or build only one new ring. Accordingly, the rings present in many combinatorial libraries are isolated from each other, and there are few combinatorial approaches to polycyclic systems.

The synthesis of libraries of natural product analogues can be a very efficient way to learn about the structure/activity relationship of biologically active natural compounds and in so doing discover analogues with superior properties to the parent.[3] Many natural products contain interlocked rings, and the combinatorial synthesis of such molecules by methods used for de novo library synthesis is not always easy. The natural product (or a late synthetic intermediate with the complete ring system) could be used as a "core" on which to adorn assorted functionality in the last steps of the synthesis, but this requires the complete (or nearly complete) synthesis of the natural product, and a new synthesis must be undertaken to make any modifications to the core.

The synthesis of libraries of natural product analogues containing interlocked rings demands the late stage assembly of the polycyclic core from readily available building blocks in a few steps. These constraints put a premium on the use of cascade reactions for making polycyclic ring systems.[4] We report herein an improved variant of our recently introduced cascade radical annulation approach to the natural product mappicine. This variant is used to make 128 analogues (64 racemates) of mappicine and 48 analogues of the related mappicine ketone by solution phase parallel synthesis.

The metabolite (*S*)-mappicine **1** (see Figure 1) was originally isolated from *Mappa foetida* by Miers 26 years ago.[5] Its oxidized analogue mappicine ketone (**2**), although already known, was isolated from *Nothapodytes foetida* and named nothapodytine B in 1996. The methoxy analogue nothapodyne A (**3**) was also described.[6] Mappicine ketone is an antiviral lead compound with activity against herpes viruses (HSV) and human cytomegalovirus (HCMV) in the low micromolar range (3−13 μM).[7] However, little is known about the structure/activity relationship, and analogues with improved activity are needed since mappicine ketone itself is not sufficiently potent.

Several syntheses of mappicine and mappicine ketone have been introduced, and some of these are adequate for producing new analogues.[8] However, convergent synthetic routes that rapidly produce a diverse assortment of analogues are still needed. Most of the few known analogues of mappicine ketone have been produced by decarboxylation of analogous camptothecin analogues.[9] This degradative approach is useful when a suitable camptothecin derivative is in hand, but it does not provide a general solution to the analogue problem because camptothecin is more complex (and hence more difficult to make) than mappicine.

The radical cascade strategy to mappicine is summarized in Figure 2. The strategy is directly related to our route to the camptothecin class of antitumor agents.[10] In addition to

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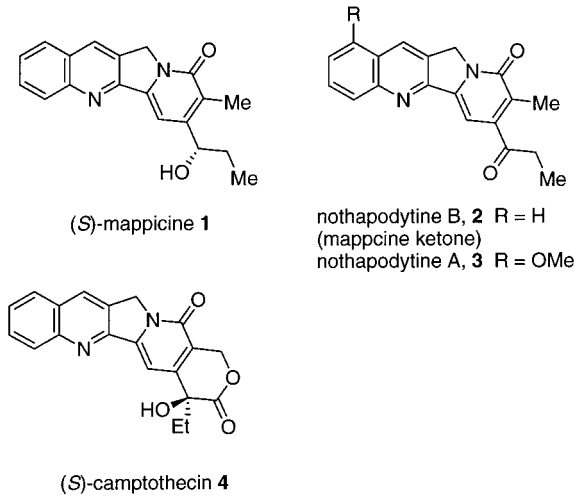


Figure 1. Natural products in the mappicine family.

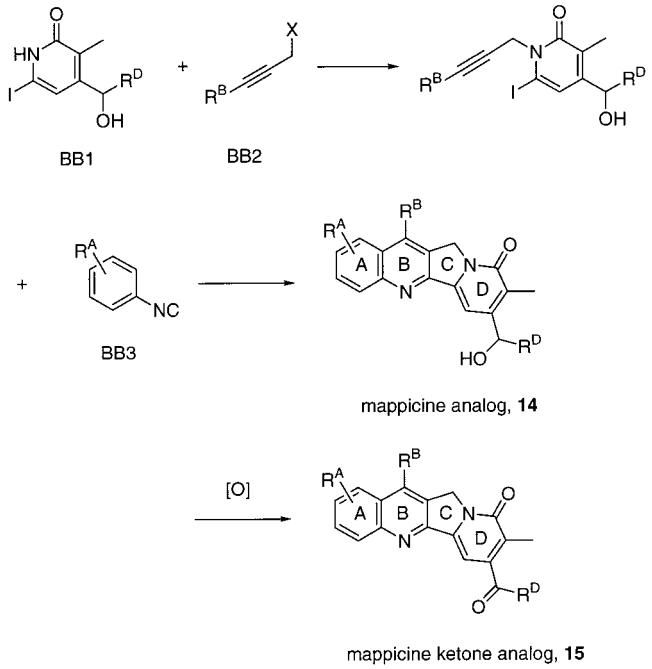
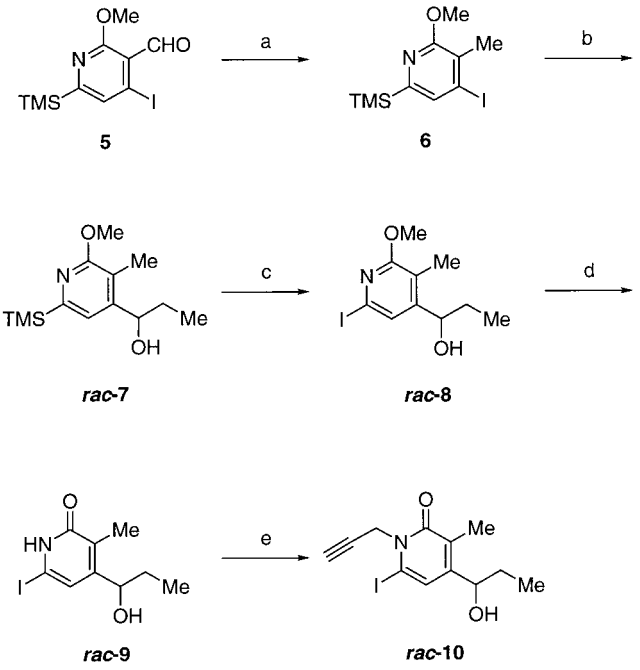


Figure 2. Building blocks in the combinatorial synthesis.

making new analogues of mappicine and mappicine ketone, a secondary goal of this work was to establish parallel synthesis techniques that could then be applied to make combinatorial libraries of camptothecin analogues. The synthesis design permits the combinatorialization of three building blocks (**BB**'s) in the last two steps. A pyridone D-ring (**BB1**) is first alkylated with a suitable propargylating agent (**BB2**) bearing the B-ring substituent. Cascade radical annulation with an isonitrile bearing the A-ring substituent (**BB3**) then produces the mappicine analogue. Mappicine ketone analogues appear more important at this point since they have shown the antiviral activity, and these are produced from the mappicine analogues by parallel oxidation.

We have already described the synthesis of (*S*)-mappicine and mappicine ketone following this general approach.[11] However, the yield of the key cascade radical reaction was low (30%), and mappicine was obtained in only 60% enantiomeric excess. By analogy to related work, we anticipated that the yield of the radical annulation could be

Scheme 1[a]



[a] Reagents and conditions: (a) Et_3SiH, $BF_3{\cdot}OEt_2$, 60 °C, 73%; (b) ^{i}PrMgCl, THF, −40 °C then EtCHO, 87%; (c) ICl, CH_2Cl_2−CCl_4, 23 °C, 48% (92% based upon recovered **7**); (d) TMSCl, NaI, MeCN, H_2O, 65 °C, 80%; (e) NaH, LiBr, DME−DMF, 0 °C then propargyl bromide, 70 °C, 86%.

improved by replacing the bromopyridone used in the original synthesis with a more reactive iodopyridone.[10] Thus, prior to synthesizing libraries, we set out to improve our existing synthesis of mappicine.

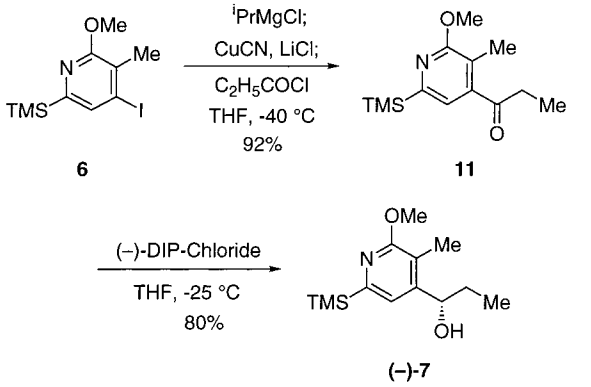
Results and Discussion

Improved Synthesis of Mappicine. Our first goal was the preparation of iodopyridone **10**, and this is outlined in Scheme 1. Starting from the known formyl pyridine **5**,[7] reduction of the aldehyde with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$[12] afforded **6**, which after transmetalation with ^{i}PrMgCl to form the heteroaryl Grignard reagent[13] and quenching with propionaldehyde gave rise to ***rac*-7**. Following the same steps used in the synthesis of (20*S*)-camptothecin,[7b] TMS-iodine exchange, demethylation, and *N*-propargylation provided the iodopyridone ***rac*-10** in an overall yield of 40%. The ease of the introduction of the side chain by Grignard chemistry (**6** → **7**) allows the facile preparation of other D-ring building blocks for library synthesis.

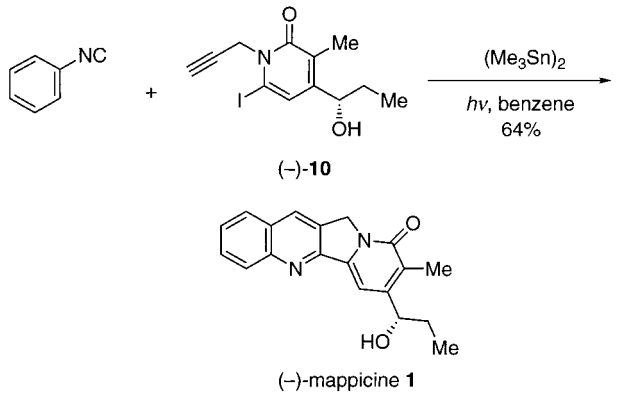
We also modified the synthesis to provide enantiomerically pure (*S*)-mappicine, as shown in Scheme 2. Quenching the cuprate reagent derived from **6** with propionyl chloride[14] afforded the ketone **11** in 92% yield. Reduction of this ketone with [(−)-*B*-chlorodiisopinocamphenylborane] [(−)-DIP-chloride[15]] gave rise to **(−)-7** as a single enantiomer according to analysis by formation of the Mosher ester (>95% ee). The same transformations as used in the racemic series were then followed to make **(−)-10** (see Scheme 1).

Finally, the radical cyclization with **(−)-10** and phenylisonitrile in the presence of hexamethylditin in benzene afforded (−)-mappicine **1** in 64% yield (Scheme 3). Racemic

Scheme 2



Scheme 3



mappicine was obtained with similar yield (63%) using ***rac*-10**. As expected,[10c] the substitution of bromine by iodine in the halopyridone radical precursor resulted in a 2-fold increase in the yield of the cascade radical reaction.

Parallel Synthesis of Libraries. With the improved synthesis of mappicine in hand, we pursued the synthesis of mappicine libraries. To illustrate the potential of this route, we conducted four separate parallel synthesis experiments in a $4 \times 4 \times 1$ manner by using 4 different isonitriles (**BB3**), 4 different propargyl bromides (**BB2**), and one iodopyridone (**BB1**). Each of the four library experiments with a different iodopyridone employed the same four propargyl bromides and four isonitriles. This results in a $4 \times 4 \times 4$ library of 64 mappicine analogues. Racemic iodopyridones **10** were used so the resulting 64 products are racemates. In the HIV area, the main interest is in mappicine ketone, not mappicine, and it is unclear whether any analogues of mappicine itself will be active. If active racemic samples are discovered, then the asymmetric route can be used to prepare single enantiomers for evaluation.

The building blocks **9**, **11**, and **12** for the library are shown in Figure 3 along with general and specific examples of the products **13**−**15** prepared by the route outlined in Figure 2. We first prepared four iodopyridones **9**{*1*−*4*} by the method in Scheme 1 starting with the appropriate reagents. Each iodopyridone **9**{*1*−*4*} was reacted with the four propargyl bromides **11**{*1*−*4*} in a traditional (that is, nonparallel) manner. The 16 products **13**{*1*−*4*,*1*−*4*} were purified by flash chromatography and fully characterized.

An initial 16-member mappicine library **14**{*1*,*1*−*4*,*1*−*4*} was made in parallel in a semiautomated fashion starting

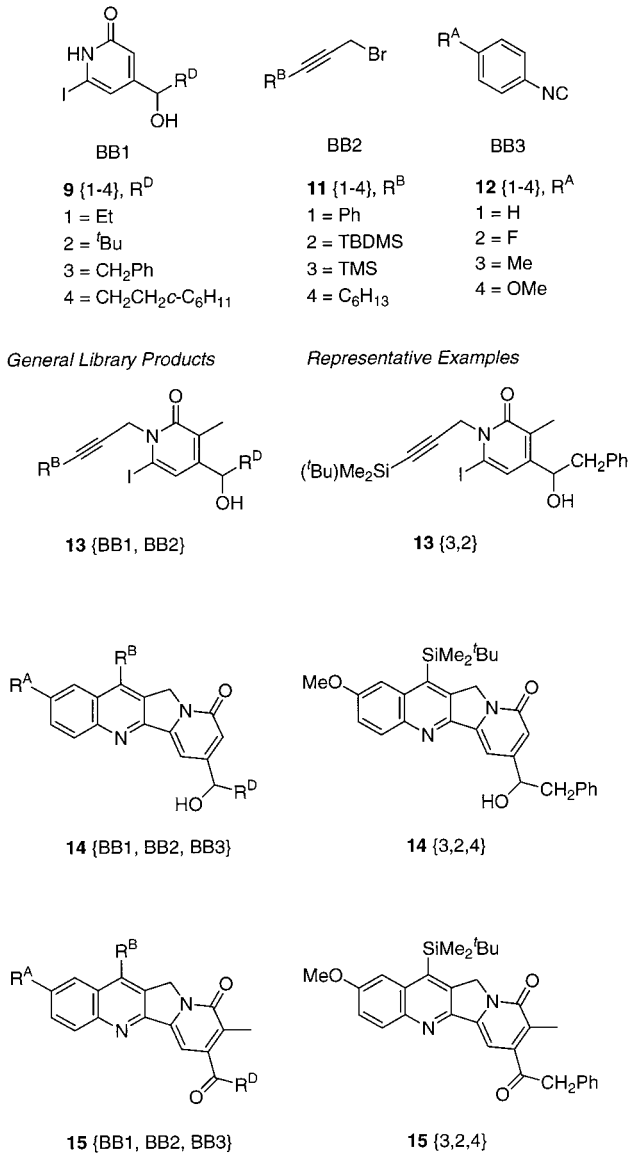


Figure 3. Library building blocks.

from iodopydridones **13**{*1*,*1*−*4*}. A Hewlett-Packard automatic synthesizer[16] was programmed to combine and mix benzene stock solutions of the reagents into 16 different vials. These vials were then manually removed from the robot, placed in front of a sunlamp, irradiated simultaneously for 10−12 h, and then returned to the robot. In some cases, a precipitate was observed in the vials at this stage, and this is thought to be the product. The solvent was evaporated, and CH_2Cl_2 was added to dissolve the precipitate. This crude solution was robotically purified using a prepacked silica gel cartridge by eluting with CH_2Cl_2 to remove the isonitrile and tin impurities and then with CH_2Cl_2-acetone to elute each mappicine analogue.[17]

The yields and purities of the initial 16-member library **14** after solid phase extraction (SPE) are shown in Table 1 under the heading "SPE yield". There were no failures; all 16 of the reactions provided the corresponding mappicine analogues as assayed by LCMS and NMR spectroscopy of selected members (see Experimental Section). Yields are typically in the range of 60−80%, and purities vary from 70 to 90%. It took about 60 min for the robot to conduct

Table 1. Yield and Purities of Initial Mappicine Library **14**{*1,1−4,1−4*} with R^D = Et

entry	no.[a]	R^A	R^B	SPE yield[b] **14**	SPE purity[c] **14**	purified yield[d] **14**	MS[e]
1	**14**{*1,1,1*}	H	Ph	75	77	58	383
2	**14**{*1,1,2*}	F	Ph	80	76	61	401
3	**14**{*1,1,3*}	Me	Ph	78	77	60	397
4	**14**{*1,1,4*}	OMe	Ph	77	74	57	413
5	**14**{*1,2,1*}	H	TBDMS	67	67	45	421
6	**14**{*1,2,2*}	F	TBDMS	69	75	52	439
7	**14**{*1,2,3*}	Me	TBDMS	70	81	56	435
8	**14**{*1,2,4*}	OMe	TBDMS	73	81	59	451
9	**14**{*1,3,1*}	H	TMS	74	57	47	379
10	**14**{*1,3,2*}	F	TMS	71	85	60	397
11	**14**{*1,3,3*}	Me	TMS	63	79	50	393
12	**14**{*1,3,4*}	OMe	TMS	60	98	59	409
13	**14**{*1,4,1*}	H	C_6H_{13}	79	73	58	391
14	**14**{*1,4,2*}	F	C_6H_{13}	76	75	57	409
15	**14**{1,4,3}	Me	C_6H_{13}	81	72	58	405
16	**14**{*1,4,4*}	OMe	C_6H_{13}	78	77	60	421

[a] **14** {**9**(R^D), **11** (R^B), **12** (R^A)}. [b] Crude yield after robotic solid phase extraction. [c] SPE purity = SPE yield ÷ purified yield. [d] After flash chromatography. [e] ESMS, *m/e*, M + 1.

each solid phase extraction, so the coarse purification of each library could be achieved in less than a day. Although the ^{1}H NMR spectra of the crude new derivatives appeared rather clean in the aromatic and benzylic regions of the spectrum, there were often some impurities in the upfield region (presumably derived from the tin reagent). While these crude products might be useful for some types of biological testing, we were interested in obtaining pure products to accurately gauge the overall efficiency of the parallel synthesis. Accordingly, each member of the first library of 16 products **14**{*1,1−4,1−4*} was purified by flash chromatography, and the isolated yields of pure products are shown in Table 1 under the heading "purified yield". The modest decreases in yields after purification confirmed the initial purity assessment.

Due to their antiviral activity, mappicine ketones are of more immediate interest than mappicine. Accordingly, we developed a method for the parallel oxidation of mappicines **14** to mappicine ketones **15**. Since we had already purified the library once, we set as a goal for the oxidation step the identification of a parallel method that gave crude products of sufficient purity for testing without rechromatography. Although the oxidation of mappicine **1** to mappicine ketone **2** is well-known, the standard methods were not suitable for our needs. We therefore surveyed the oxidation of (±)-mappicine with six polymer-supported oxidant reagents,[18] and the results of this survey are summarized in Table 2.

The oxidation with the supported reagents derived from PCC[19] and PDC[20] (entries 1 and 2) did not go to completion, even with a very large excess of reagent (more that 100 equiv) and at high temperatures. No oxidation occurred with the reagent derived from $KMnO_4$[21] (entry 3), and when we employed the recently published method of resin trapping by oxidation with Dess−Martin periodinane (DMP),[22] the crude product was not sufficiently pure (entry 4). Finally, the oxidation was achieved using the resins derived from perruthenate[23] (entry 5) or chromic acid[24] (entry 6) in refluxing toluene for 12 h. After filtration and washing of the resin, mappicine ketone **2** was obtained in high yield (87 and 92%) and good purity. Because the resin derived from chromic acid was cheaper and commercially available, we used it to oxidize the mappicine library.

Table 2. Trial Oxidations of **14**{*1,1,1*} to **15**{*1,1,1*} with Supported Oxidants[a]

Entry	Oxidant	Conditions	Yield
1		DCE, 80 °C, 24 h PhMe, 100 °C, 24 h	Mixture **14**:**15** (*ca.* 1:1)
2		DCE, 80 °C, 24 h PhMe, 100 °C, 24 h	Mixture **14**:**15** (*ca.* 1:1)
3		PhMe, 100 °C, 24 h	**14**
4		CH_2Cl_2, 23 °C, 12 h	**15** + impurities
5		PhMe, 100 °C, 12 h	**15** (87%)
6		PhMe, 100 °C, 12 h	**15** (92%)

[a] PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; DMP, Dess−Martin periodinane; DGE, 1,2-dichloroethane.

Table 3. Yields of Mappicine Ketones **15**{*1,1−4,1−4*} from Oxidation of **14** (R^D = Et)

entry	no.[a]	R^A	R^B	ketone yield[b]	MS[c]
1	**15**{*1,1,1*}	H	Ph	82	379
2	**15**{*1,1,2*}	F	Ph	86	397
3	**15**{*1,1,3*}	Me	Ph	85	393
4	**15**{*1,1,4*}	OMe	Ph	89	409
5	**15**{*1,2,1*}	H	TBDMS	85	417
6	**15**{*1,2,2*}	F	TBDMS	84	435
7	**15**{*1,2,3*}	Me	TBDMS	86	431
8	**15**{*1,2,4*}	OMe	TBDMS	91	447
9	**15**{*1,3,1*}	H	TMS	90	375
10	**15**{*1,3,2*}	F	TMS	87	393
11	**15**{*1,3,3*}	Me	TMS	83	384
12	**15**{*1,3,4*}	OMe	TMS	87	405
13	**15**{*1,4,1*}	H	C_6H_{13}	86	387
14	**15**{*1,4,2*}	F	C_6H_{13}	88	405
15	**15**{*1,4,3*}	Me	C_6H_{13}	83	401
16	**15**{*1,4,4*}	OMe	C_6H_{13}	79	417

[a] **15** {**9**(R^D), **11** (R^B), **12** (R^A)}. [b] Crude yield, single peak in LC by MS and UV detection. [c] ESMS, *m/e*, M − 1.

The parallel oxidation of the initial 16-member library of mappicine analogues was conducted on an argonaut solid phase synthesizer (Quest 210). To minimize problems arising with evaporation of the solvent during heating, we carried out these oxidations in xylenes. The procedure was very simple. After mixing the reaction components in each separate vessel and heating at 100 °C, the resin was washed with CH_2Cl_2, and the solvent was evaporated on a vacuum centrifuge to yield the 16 different mappicine ketones with high yields and purities (single peak in LCMS). The data for this library experiment are shown in Table 3.

With this initial library in hand, we then set out to prepare three analogous libraries starting from iodopyridones **13**{*2−4*} and the same four isonitriles. Although we encountered a significant technical problem (see below), we were nonetheless able to isolate pure products in all three of the mappicine libraries and in two of the three mappicine ketone

Table 4. Yields of Mappicines **14**{*2*−*4*,*1*−*4*,*1*−*4*}

14[a]	%yield[b]	MS[c]	**14**[a]	%yield[b]	MS[c]
{*2*,*1*,*1*}	60/29	409	{*3*,*3*,*1*}	61/32	459
{*2*,*1*,*2*}	58/25	427	{*3*,*3*,*2*}	64/28	477
{*2*,*1*,*3*}	68/31	423	{*3*,*3*,*3*}	59/25	473
{*2*,*1*,*4*}	62/25	439	{*3*,*3*,*4*}	60/30	489
{*2*,*2*,*1*}	52/34	447	{*3*,*4*,*1*}	78/19	471
{*2*,*2*,*2*}	64/30	465	{*3*,*4*,*2*}	73/29	489
{*2*,*2*,*3*}	68/19	461	{*3*,*4*,*3*}	63/31	485
{*2*,*2*,*4*}	72/21	477	{*3*,*4*,*4*}	60/28	501
{*2*,*3*,*1*}	69/26	405	{*4*,*1*,*1*}	79/40	443
{*2*,*3*,*2*}	57/20	423	{*4*,*1*,*2*}	63/31	461
{*2*,*3*,*3*}	60/28	419	{*4*,*1*,*3*}	83/28	457
{*2*,*3*,*4*}	65/33	435	{*4*,*1*,*4*}	72/29	473
{*2*,*4*,*1*}	65/35	417	{*4*,*2*,*1*}	51/21	481
{*2*,*4*,*2*}	55/36	435	{*4*,*2*,*2*}	59/23	499
{*2*,*4*,*3*}	55/35	431	{*4*,*2*,*3*}	62/25	495
{*2*,*4*,*4*}	73/31	447	{*4*,*2*,*4*}	64/25	511
{*3*,*1*,*1*}	60/33	463	{*4*,*3*,*1*}	64/34	439
{*3*,*1*,*2*}	64/32	481	{*4*,*3*,*2*}	71/33	457
{*3*,*1*,*3*}	65/35	477	{*4*,*3*,*3*}	77/21	453
{*3*,*1*,*4*}	56/21	493	{*4*,*3*,*4*}	63/29	469
{*3*,*2*,*1*}	48/18	501	{*4*,*4*,*1*}	59/29	451
{*3*,*2*,*2*}	74/39	519	{*4*,*4*,*2*}	67/35	469
{*3*,*2*,*3*}	57/21	515	{*4*,*4*,*3*}	72/28	465
{*3*,*2*,*4*}	60/23	531	{*4*,*4*,*4*}	64/26	481

[a] **14** {**9**(R^D), **11** (R^B), **12** (R^A)}. [b] Crude yield/purified yield after serial HPLC (see text). [c] ESMS, *m*/*e*, M+1.

Table 5. Yields of Purified Mappicine Ketone **15**{*2*,*1*−*4*,*1*−*4*} and **15**{*4*,*1*−*4*,*1*−*4*}

15[a]	yield[b]	MS[c]	**15**[a]	yield[b]	MS[c]
{*2*,*1*,*1*}	40	407	{*4*,*1*,*1*}	35	461
{*2*,*1*,*2*}	46	425	{*4*,*1*,*2*}	38	479
{*2*,*1*,*3*}	25	421	{*4*,*1*,*3*}	41	475
{*2*,*1*,*4*}	36	437	{*4*,*1*,*4*}	31	491
{*2*,*2*,*1*}	38	445	{*4*,*2*,*1*}	26	499
{*2*,*2*,*2*}	31	463	{*4*,*2*,*2*}	39	517
{*2*,*2*,*3*}	32	459	{*4*,*2*,*3*}	31	513
{*2*,*2*,*4*}	32	475	{*4*,*2*,*4*}	33	525
{*2*,*3*,*1*}	21	403	{*4*,*3*,*1*}	49	457
{*2*,*3*,*2*}	25	421	{*4*,*3*,*2*}	39	475
{*2*,*3*,*3*}	29	417	{*4*,*3*,*3*}	42	471
{*2*,*3*,*4*}	37	433	{*4*,*3*,*4*}	46	487
{*2*,*4*,*1*}	42	415	{*4*,*4*,*1*}	39	469
{*2*,*4*,*2*}	40	433	{*4*,*4*,*2*}	36	487
{*2*,*4*,*3*}	38	429	{*4*,*4*,*3*}	25	483
{*2*,*4*,*4*}	29	445	{*4*,*4*,*4*}	38	499

[a] **14** {**9**(R^D), **11** (R^B), **12** (R^A)}. [b] Yields are of product purified by serial HPLC and are overall from **13**, including the radical reaction losses due to contamination and oxidation. [c] ESMS, *m*/*e*, M − 1.

libraries. The data for these libraries are shown in Tables 4 and 5, respectively.

The three mappicine libraries were made sequentially by the robotic method described above. The yields of the 48 crude products **14**{*2*−*4*,*1*−*4*,*1*−*4*} are shown in Table 5 and were comparable to the initial library (as were the purities). The identities of all 48 products were confirmed by LCMS. The technical problem interposed when we decided to purify all 48 products by automated serial HPLC. The crude products were injected in THF and then purified using a gradient of methanol/water to pure methanol (see Experimental Section). Samples were collected by autodetection using a UV detector. Unexpectedly, the weights of the "purified" samples routinely exceeded those of the crude samples by 10−20% or more. The added impurity was traced to the THF used for injection and is believed to be a peroxide resulting from THF autooxidation.

At this point, the libraries of contaminated products were divided roughly in half. Half of each compound was repurified under the above conditions (using DMSO for injection) to give the 48 pure mappicine products in the yields listed in Table 4. These yields are considerably lower than those in the first library, but adequate quantities of all the products were obtained for biological testing. The other half of each sample (still containing the peroxide impurity) was directly oxidized as described above. The library of mappicine analogues derived from **14**{*3*,*1*−*4*,*1*−*4*} (R^D = benzyl) did not provide clean mappicine ketone products in any case (as assayed by selected NMR spectra and LCMS), and these 16 product mixtures were not purified. The other 32 oxidations worked well, and the crude products were then purified by serial HPLC to give the isolated yields shown in Table 5. These yields are again considerably lower than the first library and reflect the problems with the contaminated THF. Nonetheless, the final mappicine ketones are not contaminated, and the quantities were again sufficient for testing.

Conclusions

We have developed an improved cascade radical annulation approach to both racemic and enantiopure mappicine and mappicine ketone. We have also prepared the first library of mappicines (64 racemates) and mappicine ketones (48) in a parallel synthesis fashion. The ease of the synthesis and the ready availability of precursors for the three key building blocks lays the groundwork for the synthesis of large numbers of analogues to help elucidate the structure/activity relationships in this series of compounds. Low-level automation is essential for the purification and characterization of the libraries, but no special techniques of purification or isolation are needed.

As an aside, we learned the lesson that parallel synthesis multiplies not only the number of products that are made but also the magnitude of otherwise minor technical problems. Had we been working in a traditional serial mode, we would have discovered the problem of the contaminated THF after the synthesis of the first one or two analogues. The problem would have been quickly corrected, and the rest of the analogues made in a proper manner. But the automated methods were so straightforward to conduct that we already had 48 samples processed before the problem was identified. Given the goal of isolation of the pure products, it made more sense at that point simply to purify the contaminated products rather than to repeat the library synthesis. What we sacrificed in taking this decision was accurate yield information.

In the past, strategies for total synthesis of polycyclic natural products have typically focused on the final target alone or on a series of very closely related analogues which were made by postsynthesis derivitization of the natural product or a very late stage intermediate. The increasing ability to conduct reactions in parallel provides a strong incentive to design synthetic strategies toward polycyclic

molecules that involve the late stage construction of the core of the molecule with a cascade of reactions. As illustrated by the syntheses of mappicine and mappicine ketone outlined herein, such strategies can readily be adapted for natural products library synthesis. We are currently applying the methods reported herein to the synthesis of libraries of camptothecin analogues.

Experimental Section

4-Iodo-2-methoxy-3-methyl-6-trimethylsilylpyridine (6). To a solution of 4-iodo-2-methoxy-6-trimethylsilyl-3-pyridinecarboxaldehyde **5** (1.28 g, 3.83 mmol) and Et_3SiH (1.6 mL, 6.13 mmol) cooled to 0 °C was added dropwise $BF_3 \cdot OEt_2$ (1.26 mL, 6.13 mmol). Then the mixture was stirred 2 h at 60 °C. After cooling, brine was added and the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (hexanes) to give **6** as a colorless oil (896 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 3.96 (s, 3H), 2.33 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 160.9, 132.6, 124.3, 112.8, 53.7, 20.8, −1.9; HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}INOSi$ (M^+) 321.0034, found 321.0046; EIMS *m*/*z* 321 (M^+, 57), 306 (100).

1-[2-Methoxy-3-methyl-6-(trimethylsilanyl)pyridin-4-yl]-propan-1-one (11). To a solution of **6** (2.70 g, 8.4 mmol) in THF (27 mL) at −40 °C was added dropwise ^{i}PrMgCl (1.5 equiv, 6.3 mL, 2.0 M in THF). The solution was stirred at that temperature for 30 min, and then CuCN·2LiCl [10.1 mmol, 1.2 equiv; prepared from CuCN (985 mg, 1.2 equiv) and LiCl (933 mg, 2.4 equiv)] in THF (11 mL) was added. After 5 min, propionyl chloride (1.56 mg, 1.46 mL, 16.8 mmol) was added, and the reaction was stirred 1 h at −40 °C and 15 min at 23 °C. It was diluted with Et_2O, washed with brine, and extracted with Et_2O. The combined organic layers were dried and evaporated, and the residue was subjected to flash chromatography (hexanes−EtOAc 200:1) affording **11** as a colorless oil (1.94 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 3.97 (s, 3H), 2.82 (q, J = 7.4 Hz, 2H), 2.17 (s, 3H), 1.18 (t, J = 7.4 Hz, 3H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 162.4, 162.1, 147.1, 118.6, 116.7, 53.5, 36.2, 12.4, 7.9, −1.8; HRMS (EI) *m*/*z* calcd for $C_{13}H_{21}NO_2Si$ (M^+) 251.1340, found 251.1342; EIMS *m*/*z* 251 (M^+, 36), 236 (100), 73 (71).

***(S)*-1-[2-Methoxy-3-methyl-6-(trimethylsilanyl)pyridin-4-yl]propan-1-ol {(−)7}.** A solution of **11** (332 mg, 1.32 mmol) and [(−)-*B*-chlorodiisopinocamphenylborane, DIP-chloride] (759 mg, 2.5 mmol) in THF (2.5 mL) was stirred at −25 °C for 20 h. After that, it was warmed to 0 °C and NaOH (3 mL, 3M) and H_2O_2 30% (4 mL) were added, and the mixture was stirred at 23 °C for 12 h. Then it was diluted with Et_2O, washed with brine, extracted with Et_2O, and evaporated. The residue was purified by flash chromatography (hexanes−EtOAc 20:1) to give **(−)-7** as a colorless oil (264 mg, 80%): $[\alpha]^{23}_D$ = −24.9 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 4.88 (t, J = 6.4 Hz, 1H), 3.98 (s, 3H), 2.13 (s, 3H), 1.92 (br s, 1H), 1.71 (quint, J = 7.0 Hz, 2H), 0.99 (t, J = 7.0 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 164.5, 154.1, 122.3, 119.5, 74.9, 56.7, 34.1, 14.2, 13.7, 1.7; HRMS (EI) *m*/*z* calcd for $C_{13}H_{23}NO_2Si$ (M^+): 253.1499, found 253.1498; EIMS *m*/*z* 253 (M^+, 25), 238 (100).

General Procedure for Grignard Formation and Addition to Aldehydes. To a solution of iodopyridine **6** (3 mmol) in THF (10 mL) at −40 °C was added dropwise ^{i}PrMgCl (1.3 equiv, 2.0 M in THF). The solution was stirred at that temperature for 30 min, then the aldehyde (1.6 equiv) was added neatly, and the reaction was stirred 1 h at −40 °C and 15 min at 23 °C. It was diluted with Et_2O, washed with brine, and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated, and the residue was subjected to flash chromatography.

1-[2-Methoxy-3-methyl-6-(trimethylsilanyl)pyridin-4-yl]-2,2-dimethyl-propan-1-ol: colorless oil (74%), flash chromatography (hexanes−EtOAc 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 4.75 (d, J = 3.1 Hz, 1H), 3.96 (s, 3H), 2.13 (s, 3H), 1.87 (d, J = 3.1 Hz, 1H), 0.90 (s, 9H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 159.6, 148.4, 121.5, 118.1, 76.3, 53.3, 36.9, 26.1, 12.4, −1.7; HRMS (EI) *m*/*z* calcd for $C_{15}H_{27}NO_2Si$ (M^+) 281.1811, found 281.1800; EIMS *m*/*z* 281 (M^+, 23), 266 (36), 225 (100).

3-Cyclohexyl-1-[2-methoxy-3-methyl-6-(trimethylsilanyl)pyridin-4-yl]propan-1-ol: colorless oil (72%), flash chromatography (hexanes−EtOAc 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 4.86 (t, J = 6.2 Hz, 1H), 3.97 (s, 3H), 2.11 (s, 3H), 2.02 (br s, 1H), 1.69−1.62 (m, 6H), 1,41−1.35 (m, 2H), 1.37−1.17 (m, 6H), 0.92−0.86 (m, 3H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 161.1, 151.1, 118.9, 116.0, 70.6, 66.0, 53.4, 37.7, 35.3, 33.7, 33.5, 33.3, 26.7, 26.5, 19.0, 15.4, 10.9, −1.6; HRMS (EI) *m*/*z* calcd for $C_{19}H_{33}NO_2Si$ (M^+) 335.2281, found 335.2273; EIMS *m*/*z* 335 (M^+, 23), 320 (100), 238 (41), 225 (50).

1-[2-Methoxy-3-methyl-6-(trimethylsilanyl)pyridin-4-yl]-2-phenylethanol: colorless oil (69%), flash chromatography (hexanes−EtOAc 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.23 (m, 6H), 5.10 (dd, J = 8.6, 3.8 Hz, 1H), 4.01 (s, 3H), 3.00 (dd, J = 13.9, 3.8 Hz, 1H), 2.85 (dd, J = 13.8, 8.6 Hz, 1H), 2.13 (s, 3H), 2.09 (br s, 1H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 161.3, 149.9, 138.0, 129.6, 128.8, 126.9, 119.0, 116.0, 71.3, 53.4, 44.5, 10.9, −1.6; HRMS (EI) *m*/*z* calcd for $C_{18}H_{25}NO_2Si$ (M^+) 315.1654, found 315.1650; EIMS *m*/*z* 315 (M^+, 16), 300 (33), 224 (26), 73 (100).

General Procedure for TMS-Iodine Exchange. (*S*)-4-(1-Hydroxy-1-propyl)-6-iodo-2-methoxy-3-methylpyridine {(−)8}. A sonicated solution of ICl (297 mg, 2.3 mmol) in CCl_4 (1.5 mL) at 0 °C was added to a solution of (−)-**7** (231 mg, 0.91 mmol) in CH_2Cl_2 (2 mL) at 0 °C and stirred protected from light for 24 h. The solution was diluted with CH_2Cl_2 and washed with aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (hexanes−EtOAc 25:1) to afford recovered (−)-**7** (89 mg, 39%) and (−)-**8** (135 mg, 48%) as a white solid: $[\alpha]^{23}_D$ = −27.4 (c = 1, $CHCl_3$); mp 57−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 4.75 (t, J = 6.4 Hz, 1H), 3.90 (s, 3H), 2.12 (br s, 1H), 2.03 (s, 3H), 1.64 (quint, J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 154.8, 124.7, 119.7, 116.2, 110.1, 70.8, 54.5, 30.6, 10.9, 10.2; HRMS (EI) *m*/*z* calcd for $C_{10}H_{14}$-

NO_2I (M^+) 307.0069, found 307.0057; EIMS *m*/*z* 307 (M^+, 100), 278 (27), 151 (31).

1-(6-Iodo-2-methoxy-3-methylpyridin-4-yl)-2,2-dimethylpropan-1-ol: white solid (56% with 41% of starting material), flash chromatography (hexanes−EtOAc 25:1); mp 64−65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 4.62 (s, 1H), 3.89 (s, 3H), 2.23 (s, 1H), 2.03 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 152.6, 126.9, 118.1, 109.1, 75.7, 54.4, 37.0, 26.0, 12.5; HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}INO_2$ (M^+) 335.0375, found 335.0382; EIMS *m*/*z* 335 (M^+, 25), 279 (100).

3-Cyclohexyl-1-(6-iodo-2-methoxy-3-methyl-pyridin-4-yl)-propan-1-ol: pale yellow solid (45% with 39% of starting material), flash chromatography (hexanes−EtOAc 25:1); mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 4.79 (t, J = 6.5 Hz, 1H), 3.92 (s, 3H), 2.01 (s, 3H), 1.69−1.57 (m, 6H), 1.38−1.32 (m, 2H), 1.26−1.10 (m, 6H), 0.87−0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 155.2, 124.6, 116.0, 110.2, 70.0, 54.4, 37.7, 35.1, 33.5, 33.5, 33.3, 26.7, 26.4, 15.3, 10.9; HRMS (EI) *m*/*z* calcd for $C_{16}H_{24}INO_2$ (M^+) 389.0852, found 389.0841; EIMS *m*/*z* 389 (M^+, 100), 279 (31).

1-(6-Iodo-2-methoxy-3-methyl-pyridin-4-yl)-2-phenylethanol: pale yellow solid (49% with 37% of starting material), flash chromatography (hexanes−EtOAc 25:1); mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.35−7.25 (m, 3H), 7.21−7.18 (m, 2H), 4.98 (dd, J = 8.8, 4.1 Hz, 1H), 3.93 (s, 3H), 2.92 (dd, J = 13.8, 4.1 Hz, 1H), 2.78 (dd, J = 13.8, 8.8 Hz, 1H), 2.22 (br s, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 153.8, 137.3, 130.0, 128.9, 127.2, 124.6, 116.1, 110.3, 70.7, 54.5, 44.4, 10.8; HRMS (EI) *m*/*z* calcd for $C_{15}H_{16}INO_2$ (M^+): 369.0226, found 369.0219; EIMS *m*/*z* 369 (M^+, 100), 277 (74).

General Procedure for Iodopyridone Formation. (*S*)-4-(1-Hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one {(−)-9}. To a solution of **(−)-8** (334 mg, 1.09 mmol) and NaI (262 mg, 1.75 mmol) in CH_3CN (3.5 mL) were added chlorotrimethylsilane (190 mg, 0.22 mL, 1.75 mmol) and H_2O (10 μL, 0.55 mmol), and the mixture was heated at 65 °C for 5 h with protection from light. After cooling, the mixture was diluted with EtOAc, washed with aqueous $Na_2S_2O_3$ and brine, extracted with EtOAc−MeOH, dried ($MgSO_4$), and evaporated. The residue was subjected to flash chromatography (CH_2Cl_2−MeOH 9:1) affording **(−)-9** (261 mg, 82%) as a white solid: $[\alpha]^{23}_D = -39.3$ (c = 1, MeOH); mp 174−175 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.96 (s, 1H), 4.69 (t, J = 6.5 Hz, 1H), 2.02 (s, 3H), 1.62 (quint, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.2, 157.3, 123.1, 118.9, 93.0, 71.5, 31.1, 11.5, 10.5; HRMS (EI) *m*/*z* calcd for $C_9H_{12}NO_2I$ (M^+) 292.9913, found 292.9909; EIMS *m*/*z* 293 (M^+, 100), 275 (35), 148 (24).

4-(1-Hydroxy-2,2-dimethylpropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (9{*2*}): pale yellow solid (92%), flash chromatography (CH_2Cl_2−MeOH 9:1); mp 186−187 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.91 (s, 1H), 4.55 (s, 1H), 2.02 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.1, 155.2, 125.4, 121.2, 91.1, 76.5, 37.9, 26.8, 13.5; HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}INO_2$ (M^+) 321.0226, found 321.0232; EIMS *m*/*z* 321 (M^+, 25), 238 (100).

4-(3-Cyclohexyl-1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (9{*4*}): white solid (85%), flash chromatography (CH_2Cl_2−MeOH 9:1); mp 178−179 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.96 (s, 1H), 4.71 (t, J = 6.9 Hz, 1H), 2.01 (s, 3H), 1.69−1.55 (m, 6H), 1.40−1.36 (m, 2H), 1.33−1.19 (m, 6H), 0.92−0.87 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.2, 157.6, 122.9, 118.9, 93.1, 70.5, 39.0, 35.6, 34.8, 34.5, 27.9, 27.6, 11.5; HRMS (EI) *m*/*z* calcd for $C_{15}H_{22}NO_2I$ (M^+) 375.0695, found 375.0701; EIMS *m*/*z* 375 (M^+, 14), 360 (100), 276 (28).

4-(1-Hydroxy-2-phenylethyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (9{*3*}): white solid (76%), flash chromatography (CH_2Cl_2−MeOH 9:1); mp 166−167 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.25−7.20 (m, 3H), 7.13−7.10 (m, 2H), 6.98 (s, 1H), 4.97 (dd, J = 6.9, 6.7 Hz, 1H), 2.96 (dd, J = 13.4, 6.9 Hz, 1H), 2.82 (dd, J = 13.4, 6.7 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.1, 154.7, 137.3, 129.3, 127.8, 126.1, 122.3, 117.5, 70.0, 43.3, 9.8; HRMS (EI) *m*/*z* calcd for $C_{14}H_{14}NO_2I$ (M^+) 355.0069, found 355.0074; EIMS *m*/*z* 355 (M^+, 7), 301 (8), 197 (24), 91 (100).

General Procedure for N-Alkylation. (*S*)-4-(1-Hydroxypropyl)-6-iodo-3-methyl-1-prop-2-ynyl-1*H*-pyridin-2-one ((−)-10). To a solution of **(−)-9** (200 mg, 0.69 mmol) in DME (2.4 mL) and DMF (0.6 mL) at 0 °C was added portionwise NaH (30 mg, 0.76 mmol, 60% in mineral oil). After 10 min, LiBr (120 mg, 1.38 mmol) was added and the cooling bath was removed. Propargyl bromide (170 mg, 0.16 mL, 80% in toluene) was added 10 min later, and the mixture was heated at 70 °C for 14 h protected from light. The reaction was cooled, diluted with EtOAc, washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (CH_2Cl_2−EtOAc 9:1) to yield **(−)-10** (195 mg, 86%) as a pale yellow solid: $[\alpha]^{23}_D = -30.5$ (c = 1, $CHCl_3$); mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 5.01 (part A of AB system, J = 17.0 Hz, 1H), 4.92 (part B of AB system, J = 17.0 Hz, 1H), 4.68−4.64 (m, 1H), 2.39 (t, J = 2.6 Hz, 1H), 1.94 (s, 3H), 1.58 (quint, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.4, 124.2, 118.7, 94.7, 73.1, 70.6, 44.4, 30.0, 12.3, 10.2 (one signal is not observed); HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}NO_2I$ (M^+) 331.0069, found 331.0067; EIMS *m*/*z* 331 (M^+, 100), 302 (20).

1-But-2-ynyl-4-(1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one: pale yellow solid (84%), mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 4.98−4.93 (m, 2H), 4.62 (t, J = 7.0 Hz, 1H), 3.46 (br s, 1H), 1.90 (s, 3H), 1.67 (s, 3H), 1.60 (quint, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ162.5, 153.2, 123.9, 118.5, 94.8, 80.8, 72.8, 70.2, 44.8, 29.7, 12.0, 9.9, 3.7; HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}NO_2I$ (M^+) 345.0225, found 345.0226; EIMS *m*/*z* 345 (M^+, 100), 316 (16).

1-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-(1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (13{*1,2*}): pale yellow solid (68%), mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 5.10 (part A of AB system, J = 16.5 Hz, 1H), 4.98 (part B of AB system, J = 16.5 Hz, 1H), 4.66−4.60 (m, 1H), 3.69 (br s, 1H), 1.87

(s, 3H), 1.66−1.52 (m, 2H), 0.88 (s, 9H), 0.84 (m, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.5, 124.0, 118.9, 99.7, 97.9, 94.7, 88.8, 70.4, 44.8, 29.9, 26.2, 16.8, 12.3, 10.1, −4.7; HRMS (EI) *m*/*z* calcd for $C_{18}H_{28}NO_2SiI$ (M^+) 445.0934, found 445.0941; EIMS *m*/*z* 445 (M^+, 13), 338 (100), 350 (44).

4-(1-Hydroxypropyl)-6-iodo-3-methyl-1-[3-(trimethylsilanyl)prop-2-ynyl]-1*H*-pyridin-2-one (13{*1,3*}): pale yellow solid (52%), mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 5.16 (part A of AB system, J = 17.0 Hz, 1H), 4.94 (part B of AB system, J = 17.0 Hz, 1H), 5.03−4.94 (m, 1H), 3.35 (br s, 1H), 1.91 (s, 3H), 1.68−1.52 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.4, 124.1, 118.8, 99.1, 94.8, 90.4, 70.5, 44.8, 29.9, 26.2, 12.3, 10.2, −0.1; HRMS (EI) *m*/*z* calcd for $C_{15}H_{22}NO_2SiI$ (M^+) 403.0464, found 403.0484; EIMS *m*/*z* 403 (M^+, 100), 338 (59).

4-(1-Hydroxypropyl)-6-iodo-3-methyl-1-(3-phenylprop-2-ynyl)-1*H*-pyridin-2-one (13{*1,1*}): white solid (69%); mp 156−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.42 (m, 2H), 7.29−7.23 (m, 3H), 7.11 (s, 1H), 5.32 (part A of AB system, J = 17.0 Hz, 1H), 5.16 (part B of AB system, J = 17.0 Hz, 1H), 4.62 (t, J = 6.5 Hz, 1H), 3.42 (br s, 1H), 1.89 (s, 3H), 1.65−1.53 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 153.5, 132.0, 128.8, 128.4, 124.3, 122.5, 118.9, 94.9, 84.7, 83.3, 70.4, 45.0, 30.0, 12.2, 10.0; HRMS (EI) *m*/*z* calcd for $C_{18}H_{18}NO_2I$ (M^+) 407.0382, found 407.0400; EIMS *m*/*z* 407 (M^+, 40), 378 (7), 115 (100).

4-(1-Hydroxypropyl)-6-iodo-3-methyl-1-non-2-ynyl-1*H*-pyridin-2-one (13{*1,4*}): white solid (83%), mp 134−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 5.05−4.89 (m, 2H), 4.62 (t, J = 6.5 Hz, 1H), 3.50 (br s, 1H), 2.13 (t, J = 6.9 Hz, 2H), 1.88 (s, 3H), 1.62−1.53 (m, 2H), 1.49−1.35 (m, 2H), 1.31−1.22 (m, 6H), 0.91 (t, J = 7.3 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 153.1, 123.9, 118.5, 94.7, 85.5, 73.7, 70.2, 44.6, 35.3, 31.2, 29.7, 28.4, 28.2, 22.5, 18.7, 14.0, 12.0, 10.0; HRMS (EI) *m*/*z* calcd for $C_{18}H_{26}NO_2I$ (M^+) 415.1008, found 415.0988; EIMS *m*/*z* 415 (M^+, 23), 344 (100), 294 (32).

1-(4,4-Dimethylpent-2-ynyl)-4-(1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one: white solid (60%), mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 5.07 (part A of AB system, J = 16.8 Hz, 1H), 4.91 (part B of AB system, J = 16.8 Hz, 1H), 4.62 (t, J = 6.4 Hz, 1H), 3.45 (br s, 1H), 1.88 (s, 3H), 1.69−1.54 (m, 2H), 1.17 (s, 9H), 0.91 (t, J = 7.3 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 153.1, 123.9, 118.6, 94.7, 93.5, 72.4, 70.2, 44.1, 30.6, 29.7, 27.4, 12.1, 9.9.

1-(4,4-Dimethylpent-2-ynyl)-4-(1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one: white solid (80%), mp 142−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.09 (part A of AB system, J = 16.9 Hz, 1H), 5.02 (part B of AB system, J = 16.9 Hz, 1H), 4.68 (t, J = 7.4 Hz, 1H), 3.35−2.45 (m, 2H), 1.98 (s, 3H), 1.71−1.56 (m, 6H), 1.01−0.92 (m, 6H).

4-(1-Hydroxy-2,2-dimethylpropyl)-6-iodo-3-methyl-1-(3-phenyl-prop-2-ynyl)-1*H*-pyridin-2-one (13{*2,1*}): white solid (80%), mp 203−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.31−7.26 (m, 3H), 7.07 (s, 1H), 5.39 (part A of AB system, J = 17.0 Hz, 1H), 5.23 (part B of AB system, J = 17.0 Hz, 1H), 4.59 (s, 1H), 2.09 (s, 3H), 1.81 (br s, 1H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 150.4, 132.0, 128.7, 128.3, 126.7, 122.6, 120.2, 93.4, 84.6, 83.4, 76.2, 44.8, 37.2, 29.8, 26.2, 14.2; HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}INO_2$ (M^+) 435.0687, found 435.0695; EIMS *m*/*z* 435 (M^+, 15), 279 (40), 149 (100).

1-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-(1-hydroxy-2,2-dimethylpropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (13-{*2,2*}): pale yellow solid (80%), mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 5.06 (br s, 2H), 4.49 (s, 1H), 2.90 (br s, 1H), 1.97 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 150.9, 126.4, 120.6, 99.9, 93.2, 88.8, 75.9, 44.7, 37.1, 26.2, 16.8, 14.3, −4.7; HRMS (EI) *m*/*z* calcd for $C_{20}H_{32}INO_2Si$ (M^+) 473.1270, found 473.1247; EIMS *m*/*z* 473 (M^+, 22), 417 (100).

4-(1-Hydroxy-2,2-dimethylpropyl)-6-iodo-3-methyl-1-[3-(trimethylsilanyl)prop-2-ynyl]-1*H*-pyridin-2-one (1{*2,3*}): pale yellow solid (49%), mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.12 (part A of AB system, J = 17.2 Hz, 1H), 4.97 (part B of AB system, J = 17.2 Hz, 1H), 4.49 (s, 1H), 3.05 (br s, 1H), 1.94 (s, 3H), 0.92 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 151.1, 126.5, 120.7, 99.2, 93.3, 90.4, 75.9, 44.7, 37.2, 26.3, 14.2, −0.1; HRMS (EI) *m*/*z* calcd for $C_{17}H_{26}INO_2Si$ (M^+) 431.0785, found 431.0778; EIMS *m*/*z* 431 (M^+, 100), 374 (75).

4-(1-Hydroxy-2,2-dimethylpropyl)-6-iodo-3-methyl-1-non-2-ynyl-1*H*-pyridin-2-one (13{*2,4*}): white solid (78%), mp 146−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.03 (part A of AB system, J = 16.8 Hz, 1H), 4.96 (part B of AB system, J = 16.8 Hz, 1H), 4.64 (s, 1H), 3.17 (br s, 1H), 2.13 (t, J = 6.9 Hz, 2H), 1.89 (s, 3H), 1.62−1.53 (m, 2H), 1.49−1.35 (m, 2H), 1.31−1.22 (m, 6H), 0.91 (s, (H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 151.2, 126.4, 120.8, 93.4, 85.7, 75.7, 74.0, 44.7, 37.1, 31.4, 28.7, 28.4, 28.2, 26.3, 22.7, 19.0, 14.2, 14.0; HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}INO_2$ (M^+) 443.1302, found 443.1321; EIMS *m*/*z* 443 (M^+, 22), 346 (100).

4-(3-Cyclohexyl-1-hydroxypropyl)-6-iodo-3-methyl-1-(3-phenyl-prop-2-ynyl)-1*H*-pyridin-2-one (13{*4,1*}): white solid (80%), mp 137−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.31−7.26 (m, 3H), 7.12 (s, 1H), 5.35 (part A of AB system, J = 17.1 Hz, 1H), 5.14 (part B of AB system, J = 17.1 Hz, 1H), 4.68−4.64 (m, 1H), 3.17 (br s, 1H), 1.90 (s, 3H), 1.62−1.49 (m, 8H), 1.29−1.02 (m, 6H), 0.89−0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 153.7, 132.0, 128.8, 128.4, 124.0, 122.5, 118.9, 94.8, 84.7, 83.4, 69.7, 44.9, 37.8, 34.5, 33.5, 33.2, 30.7, 26.7, 26.4, 12.2; HRMS (EI) *m*/*z* calcd for $C_{24}H_{28}INO_2$ (M^+) 489.1142, found 489.1164; EIMS *m*/*z* 489 (M^+,100).

1-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-(3-cyclohexyl-1-hydroxypropyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (13{*4,2*}): pale yellow solid (77%), mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H),), 5.10 (part A of AB system, J = 17.2 Hz, 1H), 5.03 (part B of AB system, J = 17.2 Hz, 1H), 4.68−4.62 (m, 1H), 3.17 (br s, 1H), 2.01 (s, 3H), 1.69−1.47 (m, 8H), 1.37−1.31 (m, 2H), 1.28−1.17

(m, 6H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.5, 123.9, 118.6, 99.8, 94.7, 88.7, 69.7, 66.0, 44.7, 37.7, 34.4, 33.5, 33.3, 26.7, 26.4, 26.2, 16.8, 15.3, 12.3, −4.7; HRMS (EI) *m/z* calcd for $C_{24}H_{38}INO_2Si$ (M^+) 527.1703, found 527.1717; EIMS *m/z* 527 (M^+,11), 470 (100).

4-(3-Cyclohexyl-1-hydroxypropyl)-6-iodo-3-methyl-1-[3-(trimethylsilanyl)prop-2-ynyl]-1*H*-pyridin-2-one (13{*4,3*}): pale yellow solid (80%), mp 121−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 5.08 (part A of AB system, J = 17.2 Hz, 1H), 5.00 (part B of AB system, J = 17.2 Hz, 1H), 4.68−4.62 (m, 1H), 3.29 (br s, 1H), 1.91 (s, 3H), 1.63−1.46 (m, 8H), 1.39−1.33 (m, 2H), 1.23−1.13 (m, 6H), 0.85−0.81 (m, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.6, 123.9, 118.7, 99.2, 94.8, 90.4, 69.6, 44.8, 37.8, 34.4, 33.5, 33.3, 26.7, 26.4, 12.3, −0.1; HRMS (EI) *m/z* calcd for $C_{21}H_{32}INO_2Si$ (M^+) 485.1250, found 485.1247; EIMS *m/z* 485 (M^+,100).

4-(3-Cyclohexyl-1-hydroxypropyl)-6-iodo-3-methyl-1-non-2-ynyl-1*H*-pyridin-2-one (13{*4,4*}): white solid (85%), mp 84-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 5.06−4.93 (m, 2H), 4.67−4.62 (m, 1H), 3.28 (br s, 1H), 2.14 (t, J = 6.9 Hz, 2H), 1.89 (s, 3H), 1.62−1.53 (m, 6H), 1.49−1.35 (m, 4H), 1.31−1.02 (m, 16H), 0.87−0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.6, 123.9, 118.6, 102.54, 95.0, 85.7, 73.9, 69.6, 44.8, 37.7, 34.4, 33.5, 33.4, 33.2, 31.4, 28.7, 28.5, 26.7, 26.4, 22.7, 19.0, 14.2, 12.2; HRMS (EI) *m/z* calcd for $C_{24}H_{26}INO_2$ (M^+) 497.1815, found 497.1791; EIMS *m/z* 497 (M^+, 22), 400 (100).

4-(1-Hydroxy-2-phenylethyl)-6-iodo-3-methyl-1-(3-phenylprop-2-ynyl)-1*H*-pyridin-2-one (13{*3,1*}): pale yellow solid (76%), mp 149-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.44 (m, 3H), 7.38−7.14 (m, 7H), 7.12 (s, 1H), 5.34 (part A of AB system, J = 17.0 Hz, 1H), 5.25 (part B of AB system, J = 17.0 Hz, 1H), 4.96−4.88 (m, 1H), 3.17 (br d, J = 7.2 Hz, 2H), 2.63 (br s, 1H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 151.9, 137.0, 132.0, 129.5, 128.8, 128.4, 127.1, 124.4, 122.5, 118.2, 95.1, 84.7, 83.4, 70.6, 44.9, 43.5, 12.2; HRMS (EI) *m/z* calcd for $C_{23}H_{20}INO_2$ (M^+) 469.0550, found 469.0538; EIMS *m/z* 469 (M^+, 38), 378 (100).

1-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-(1-hydroxy-2-phenylethyl)-6-iodo-3-methyl-1*H*-pyridin-2-one (13{*3,2*}): pale yellow solid (79%), mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.22 (m, 3H), 7.16−7.14 (2H), 7.12 (s, 1H), 5.05 (br s, 2H), 4.93-4.85 (m, 1H), 3.17 (br s, 1H), 2.84 (br d, J = 7.2 Hz, 2H, 1.87 (s, 3H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 151.9, 137.1, 129.5, 128.6, 126.9, 124.1, 118.2, 99.8, 94.8, 88.6, 70.5, 60.5, 44.7, 43.5, 26.1, 21.1, 16.7, 14.3, 12.2, -4.7; HRMS (EI) *m/z* calcd for $C_{23}H_{30}INO_2Si$ (M^+) 507.1091, found 507.1099; EIMS *m/z* 507 (M^+,14), 450 (100).

4-(1-Hydroxy-2-phenylethyl)-6-iodo-3-methyl-1-[3-(trimethylsilanyl)prop-2-ynyl]-1*H*-pyridin-2-one (13{*3,3*}): pale yellow solid (81%), mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 7.12 (s, 1H), 5.05 (part A of AB system, J = 17.0 Hz, 1H), 5.03 (part B of AB system, J = 17.0 Hz, 1H), 4.94−4.84 (m, 1H), 3.15 (br s, 1H), 2.84 (d, J = 7.2 Hz, 2H), 1.89 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 152.0, 137.1, 129.5, 128.7, 127.0, 124.1, 118.3, 99.1, 95.0, 90.3, 70.5, 66.0, 44.8, 43.5, 12.2, −0.1; HRMS (EI) *m/z* calcd for $C_{20}H_{24}INO_2Si$ (M^+) 465.0621, found 465.0628; EIMS *m/z* 465 (M^+, 100).

4-(1-Hydroxy-2-phenylethyl)-6-iodo-3-methyl-1-non-2-ynyl-1*H*-pyridin-2-one (13{*3,4*}): white solid (86%), mp 62−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.13 (m, 5H), 7.09 (s, 1H), 5.06−4.93 (m, 2H), 4.92−4.85 (m, 1H), 3.14 (br s, 1H), 2.83 (d, J = 7.2 Hz, 2H), 2.13 (t, J = 6.9 Hz, 2H), 1.85 (s, 3H), 1.51−1.19 (m, 8H), 0.87−0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 152.1, 137.3, 129.5, 128.7, 127.0, 124.2, 118.3, 95.2, 85.7, 73.9, 70.5, 44.9, 43.5, 31.4, 28.7, 28.5, 22.7, 19.0, 14.3, 12.1; HRMS (EI) *m/z* calcd for $C_{23}H_{28}INO_2$ (M^+) 477.1143, found 477.1164; EIMS *m/z* 477 (M^+, 18), 380 (100).

General Procedure for Radical Cascade Reaction: (*S*)-7-(1-Hydroxy-propyl)-8-methyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (−)-mappicine 1). A mixture of **(−)-10** (33.9 mg, 0.10 mmol), phenyl isonitrile (32 mg, 0.30 mmol, 1 M in benzene), and hexamethylditin (49 mg, 37 μL, 0.15 mmol) was irradiated with a 275 W GE sunlamp for 12 h. After cooling, the solvent was evaporated and the residue purified by flash chromatography (gradient CH_2Cl_2 to CH_2Cl_2−acetone 1:1 to CH_2Cl_2−MeOH 9:1) to yield (−)-mappicine (**1**) (20.2 mg, 64%) as a pale yellow solid: $[\alpha]^{23}_D$ = −1.9 (c = 0.1, $CHCl_3$−MeOH 4:1); mp 264-265 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (d, J =8.0 Hz, 1H), 7.46 (s, 1H), 7.36 (t, J = 7.4 Hz, 1H), 5.24 (part A of AB system, J =18.9 Hz, 1H), 5.08 (part B of AB system, J = 18.9 Hz, 1H), 4.90 (t, J =7.7 Hz, 1H), 3.70 (br s, 1H), 2.19 (s, 3H), 1.82 (quint, J = 6.8 Hz, 1H), 1.73 (quint, J = 7.0 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H).

Data for Selected Mappicines. 12-(*tert*-Butyl-dimethylsilanyl)-7-(1-hydroxy-propyl)-8-methyl-11*H*-indolizino-[1,2-*b*]quinolin-9-one: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.35 (s, 1H), 7.29 (t, J = 8.1 Hz, 1H), 5.31 (part A of AB system, J = 18.8 Hz, 1H), 5.07 (part B of AB system, J = 18.8 Hz, 1H), 4.86 (t, J = 6.3 Hz, 1H), 4.24 (br s, 1H), 2.14 (s, 3H), 1.86−1.79 (m, 1H), 1.71−1.65 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H), 0.97 (s, 9H), 0.78 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 154.7, 150.8, 147.2, 142.3, 142.2, 136.1, 132.1, 130.1, 129.2, 128.9, 126.1, 124.9, 99.3, 71.0, 52.6, 30.0, 27.2, 19.4, 12.2, 10.3, 0.0, −0.6; ESMS *m/z* 420.

2-Fluoro-7-(1-hydroxy-propyl)-8-methyl-12-(trimethylsilanyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (14{*1,2,1*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.5 Hz, J(^{1}H-^{19}F) = 6.8 Hz, 1H), 7.50 (dd, J = 8.3 Hz, J(^{1}H-^{19}F) = 2.6 Hz, 1H), 7.22 (s, 1H), 7.19−7.15 (m, 1H), 5.30 (part A of AB system, J = 18.9 Hz, 1H), 5.06 (part B of AB system, J = 18.9 Hz, 1H), 4.84 (t, J = 6.1 Hz, 1H), 4.47 (br s, 1H), 2.12 (s, 3H), 1.90−1.76 (m, 1H), 1.66−1.60 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, J(^{13}C-^{19}F) = 23.7 Hz), 158.4, 154.7, 150.5, 144.0, 142.4, 141.9, 135.4, 132.2 (d, J(^{13}C-^{19}F) = 8.6 Hz), 132.0

(d, $J(^{13}C\text{-}^{19}F) = 9.5$ Hz), 124.9, 118.7 (d, $J(^{13}C\text{-}^{19}F) = 25.8$ Hz), 111.5 (d, $J(^{13}C\text{-}^{19}F) = 22.3$ Hz), 99.1, 71.0, 51.8, 29.9, 12.2, 10.3; ESMS *m*/*z* 396.

12-Hexyl-7-(1-hydroxy-propyl)-2-methoxy-8-methyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (14{*1,4,4*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, $J = 9.2$ Hz, 1H), 7.34 (s, 1H), 7.21 (dd, $J = 9.2$, 2.6 Hz 1H), 6.56 (d, $J = 2.6$ Hz, 1H), 5.06 (part A of AB system, $J = 18.6$ Hz, 1H), 4.86 (part B of AB system, $J = 18.6$ Hz, 1H), 4.88−4.81 (m, 1H), 4.74 (br s, 1H), 3.84 (s, 3H), 2.79−2.74 (m, 2H), 2.12 (s, 3H), 1.90−1.79 (m, 1H), 1.67−1.60 (m, 1H), 1.57−1.26 (m, 8H), 0.95 (t, $J = 7.3$ Hz, 3H), 0.89−0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 157.7, 155.1, 149.3, 144.5, 142.9, 141.9, 131.4, 127.5, 127.2, 124.3, 121.7, 101.1, 99.3, 70.9, 55.2, 49.8, 31.7, 29.9, 29.7, 29.2, 22.6, 14.2, 12.3, 10.2; ESMS *m*/*z* 420.

7-(1-Hydroxy-propyl)-2,8-dimethyl-12-phenyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (14{*1,1,3*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 7.4$ Hz, 1H), 7.83 (t, $J = 7.4$ Hz, 1H), 7.69 (d, $J = 8.6$ Hz, 1H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.37 (s, 1H), 7.24−7.19 (m, 2H), 7.10 (s, 1H), 5.14 (part A of AB system, $J = 19.1$ Hz, 1H), 4.74 (part B of AB system, $J = 19.1$ Hz, 1H), 4.81 (t, $J = 7.0$ Hz, 1H), 4.55 (br s, 1H), 2.27 (s, 3H), 2.08 (s, 3H), 1.87−1.77 (m, 1H), 1.74−1.62 (m, 1H), 0.96 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 154.9, 150.9, 147.1, 142.8, 136.9, 135.0, 131.5, 129.7, 120.1, 129.0, 127.2, 126.2, 124.7, 124.5, 99.5, 90.9, 70.9, 50.3, 29.9, 21.9, 12.3, 10.3; ESMS *m*/*z* 396.

2-Fluoro-12-hexyl-7-(1-hydroxy-2,2-dimethyl-propyl)-8-methyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (14{*2,4,2*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−7.92 (m, 1H), 7.53 (s, 1H), 7.41−7.36 (m, 1H), 7.24−7.19 (m, 1H), 5.22 (part A of AB system, $J = 18.9$ Hz, 1H), 5.00 (part B of AB system, $J = 18.9$ Hz, 1H), 4.75 (s, 1H), 2.92 (t, $J = 6.7$ Hz, 1H) 2.20 (s, 3H), 1.81−1.35 (m, 8H), 1.33−130 (m, 2H), 0.99 (s, (H), 0.94−0.88 (m, 3H); ESMS *m*/*z* 408.

7-(3-Cyclohexyl-1-hydroxy-propyl)-12-hexyl-8-methyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (14{*4,4,1*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, $J = 8.3$ Hz, 1H), 7.59−7.54 (m, 2H), 7.43 (s, 1H), 7.31 (dd, $J = 7.8$, 7.6 Hz 1H), 5.15 (part A of AB system, $J = 18.8$ Hz, 1H), 4.97 (part B of AB system, $J = 18.8$ Hz, 1H), 4.93−4.88 (m, 1H), 2.96−2.82 (m, 2H) 2.15 (s, 3H), 1.81−1.15 (m, 25H), 0.92−0.88 (m, 3H); ESMS *m*/*z* 472.

General Procedure for Oxidation of Mappicines: 12-(*tert*-Butyl-dimethyl-silanyl)-2,8-dimethyl-7-propionyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (15{*1,2,3*}). To a solution of **14**{*1,2,3*} (6.3 mg, 0.015 mmol) in xylenes (2 mL) was added polymer supported chromic acid (150 mg, 25 equiv, 2.5 mmol/g), and the mixture was heated at 110 °C for 12 h using a solid phase synthesizer Argonaut Quest 210. After cooling, the resin was filtered and washed with CH_2Cl_2 (5 × 10), and the solvent evaporated to yield the mappicine ketone (5.7 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.6$ Hz, 1H), 8.00 (s, 1H), 7.60 (d, $J = 8.6$ Hz, 1H), 7.22 (s, 1H), 5.30 (s, 2H), 2.91 (q, $J = 7.1$ Hz, 2H), 2.58 (s, 3H), 2.29 (s, 3H), 1.25−1.22 (m, 3H), 0.99 (s, 9H), 0.63 (s, 6H); ESMS *m*/*z* 432.

8-Methyl-12-phenyl-7-propionyl-11*H*-indolizino[1,2-*b*]-quinolin-9-one (15{*1,2,1*}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 8.5$ Hz, 1H), 7.83 (t, $J = 8.5$ Hz, 1H), 7.58 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.29−7.22(m, 6H), 5.13 (s, 2H), 2.91 (q, $J = 7.1$ Hz, 2H), 2.29 (s, 3H), 0.92−0.80 (m, 3H); ESMS *m*/*z* 380.

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Supporting Information Available. Contains representative spectra for library products. This material is available free of charge via the Internet at http://pubs.acs.org.

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