# Synthesis of Enantiomerically Pure Hydrinden-2-ones and Benz[e]inden-2-ones via Asymmetric Alkylations of Chiral Bicyclic Lactams

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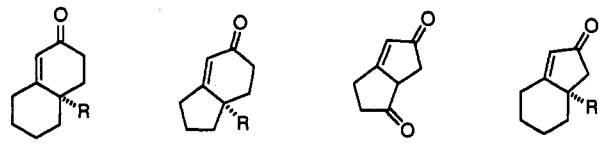
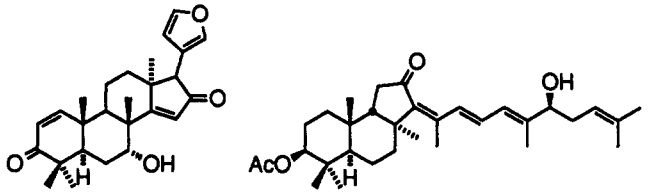
A route to the titled compounds in >99% ee was achieved from sequential diastereoselective alkylations of chiral, nonracemic bicyclic lactams **6** and **15**. An intramolecular addition of the organolithium species derived from **17a–c** and **28a–d** gave, after hydrolysis, diketones **25a–c** and **30a–d**, which were cyclized to the titled compounds **4a–c** and **31a–d**. As an example of the versatility of this method, the ABC ring system of the triterpene stelliferin A, isolated from marine organisms, was prepared in high enantiomeric excess.

Although there are a number of routes to chiral nonracemic ring systems represented by **1**, **2**,[1-4] and **3**,[5,6] there appeared prior to this study no asymmetric route to hydrinden-2-ones **4**.[7] Ring systems represented by **1** and



**1** **2** **3** **4**

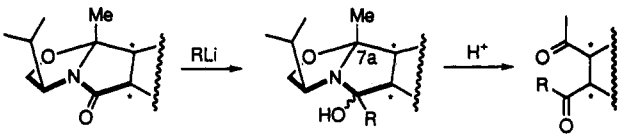
**2** have been previously prepared in enantiomerically pure form *via* the asymmetric Robinson annulation. However, in order to employ this technique for the preparation of **4**, a three-carbon acetonyl equivalent must be utilized for the construction of the enone moiety, and despite the many examples of known acetonyl equivalents,[8] they are not amenable to asymmetric annulations of the type discussed above. Since certain classes of naturally occurring compounds possess the structural unit **4**[9,10] (e.g., **A**, **B**) it was



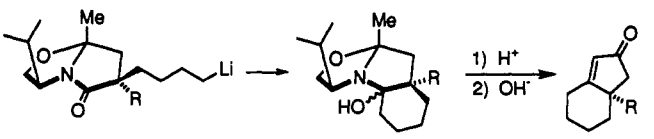
**A**: 17-Epinimbocinol **B**: Stelliferin A

deemed worthy of investigating the preparation of these bicyclo [4.3.0] systems in enantiopure form. These ring systems could be accessed from the chiral nonracemic bicyclic lactams used extensively by this group, by modifying the removal of the chiral auxilary.[11] Prior to this work the method for detaching the chiral auxiliary involved addition of an alkyllithium reagent to the lactam

**Scheme I**



**Scheme II**



**5** **4**

carbonyl followed by hydrolytic ring cleavage to furnish the optically active diketones (Scheme I).

It seemed a reasonable task to change the intermolecular alkyllithium addition to an intramolecular version, such that ring systems **4** might be accessed quite efficiently (Scheme II).[12,13] In this regard it was necessary to prepare a dialkylated bicyclic lactam wherein one of the alkyl side chains possessed a functionality which could readily be converted into an alkyllithium nucleophile (e.g., **5**).

The initial, and perhaps most obvious, approach to the preparation of the precursor to alkyllithium **5** focused on

• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

(1) Gawley, R. E. *Synthesis* **1976**, 777.

(2) Jung, M. E. *Tetrahedron Rep.* **1976**, *32*, 3.

(3) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

(4) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671.

(5) Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905.

(6) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.

(7) For racemic syntheses, see: Becker, D.; Brodsky, N. C.; Kalo, J. *J. Org. Chem.* **1978**, *43*, 2557. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 311. Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4079. Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149. Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682. Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686 and references cited therein. Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591. Smith, A. B., III; Toder, B. H.; Branca, S. J.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 1996. Hosomi, A.; Shirahata, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1981**, *46*, 4631.

(8) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4079. Hosomi, A.; Shirahata, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1981**, *46*, 4631. Jacobsen, R. M.; Raths, R. A.; McDonald, J. H., III. *J. Org. Chem.* **1977**, *42*, 2545.

(9) Tsuda, M.; Ishibashi, M.; Agemi, K.; Sasaki, T.; Kobayashi, J. *Tetrahedron* **1991**, *47*, 2181.

(10) Gaikwad, B. R.; Mayelvaganan, T.; Vyas, B. A.; Bhat, S. V. *Phytochemistry* **1990**, *29*, 3963.

(11) Romo, D.; Meyers, A. I. *Tetrahedron Rep.* **1991**, *47*, 9503.

(12) For a related example of an intramolecular halogen–metal exchange/cyclization, see: Storey, J. M. D.; McCarthy, C.; Jones, K. *J. Chem. Soc., Chem. Commun.* **1991**, 892.

(13) For a recent highly efficient method of generating organolithium reagents from the corresponding halides, see: Rawson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **1991**, *32*, 2095. General halogen–metal exchange: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

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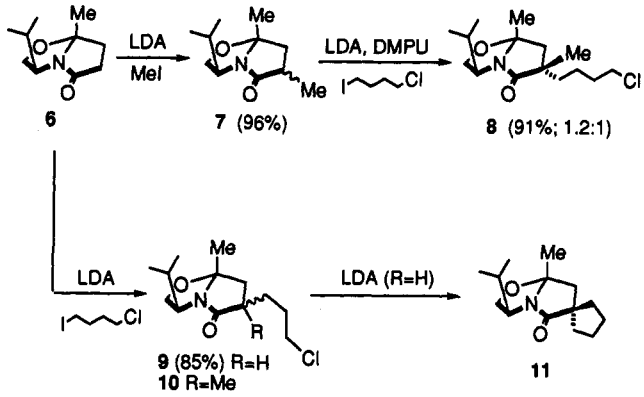
**Scheme III**

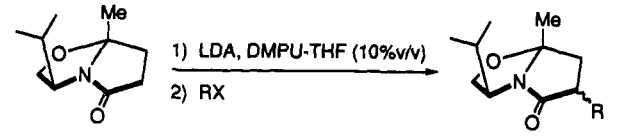



utilizing 4-chloroiodobutane as a bifunctional electrophile (Scheme III). The ω-haloalkyl side chain could then be converted to the requisite alkyllithium via halogen–metal exchange. Unfortunately, this route was disappointing as alkylation of the monomethylated lactam **7**[11] resulted in a 1.2:1 diastereomeric mixture of *endo* and *exo* adducts **8**. Considering the possibility that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU), used as a dipolar aprotic cosolvent, was responsible for the low diastereofacial selectivity, the amount of DMPU was decreased. This served only to decrease the chemical yield of the dialkylated product **8** without increasing the diastereomeric excess. Additionally, utilizing a large excess of electrophile (10 equiv) with no DMPU present provided no beneficial effect on the chemical yield. In order to assess the facial selectivity of methyl iodide addition in the second alkylation step, the order of electrophile addition was reversed. Alkylation of lactam **6** with 4-chloroiodobutane afforded excellent yields of lactam **9**. However upon regeneration of the lactam enolate, spontaneous cyclization to spiro lactam **11** was observed. This was not unexpected since intramolecular five-*exo-tet* cyclizations are well known to be extremely facile processes.[14] Because of this rapid spirocyclization, there was no means to reach the methylated product **10**, at least when a ω-haloalkyl substituent was present. Thus, other routes to **8** or **10** or their synthetic equivalent would be required.

Another problem also surfaced during the course of this study when it became necessary to seek optimum conditions for alkylation of the bicyclic lactam **6**. The conditions utilized for monoalkylation initially utilized 1.1–1.5 equiv of base for enolate formation followed by 1.5 equiv of electrophile. These conditions, however, often resulted in poor consumption of starting material, especially when employing less reactive electrophiles. It was ultimately found that a 100% excess of base allowed for a significant increase in isolated yield of monoalkylated lactam as shown in Table I. The reasons are unclear for the significant yield enhancement observed when more than a stoichiometric amount of base is employed. Since no data concerning the aggregation of the lactam enolates exist, it is difficult to speculate about the nature of this phenomenon. Suffice it to say, however, that drastic yield enhancements have been consistently observed (during *mono*alkylation) when an extra equivalent of base is utilized to generate the lactam enolate.

Since a 100% excess of base is used to generate the enolate of lactam **6**, it might be expected that bis-alkylated material should be formed. In order for bis-alkylation to occur, however, the rate of regeneration of the enolate of the monoalkylated lactams **12** must be competitive with alkylation of the enolate of lactam **6**. This is not the case, and as a result, minimal bis-alkylated product is observed under the reaction conditions. Presumably, the sterically endowed LDA is slow to reach the tertiary proton in **12**.

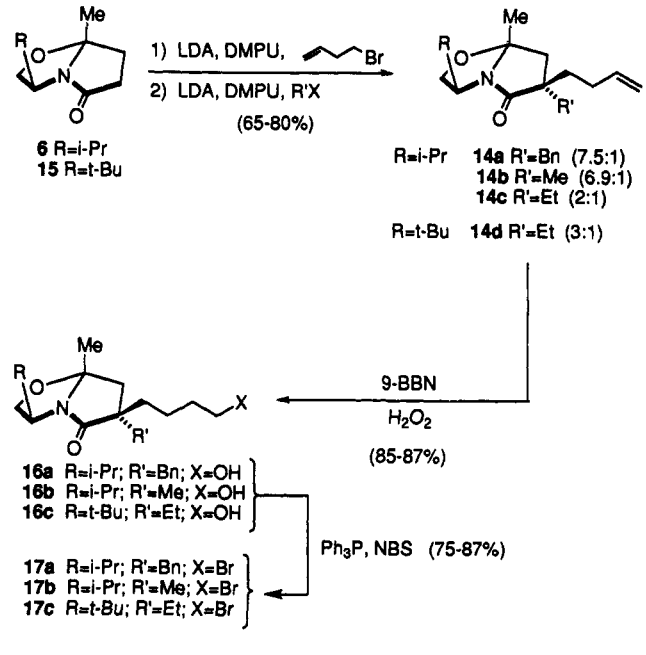
**Table I. Effect of Base on Yield of 12**




| RX | LDA (equiv) | 12/6[a] | yield (%) |
|---|---|---|---|
| I–Cl | 1.2 | 13:1 | 64 |
| | *2.0* | *>100:1* | *95* |
| Br | 1.2 | 3:1 | 75 |
| | *2.0* | *16:1* | *86* |

[a] Determined by GC analysis.

**Scheme IV**




Due to the complications described above when attempting to install the ω-halide in a single step, a slightly lengthier but rather efficient sequence was adopted.[15] Metalation–alkylation of **6** with 4-bromo-1-butene to furnish **12** (R = 3-butenyl) followed by a second metalation–alkylation sequence afforded dialkylated lactams **14a–d** in good chemical yields but with markedly varied diastereoselectivity (Scheme IV). In the case where R'X was an unactivated electrophile (i.e., iodoethane or bromobutane) poor diastereofacial selectivity was observed. In fact, under no conditions did bis-alkylation of **13** (which corresponds to the monoalkylation product of **6**) with straight-chain alkyl halides result in better than a 3:1 *endo*/*exo* ratio of lactams **14** (Table II). Other instances of low diastereofacial control of the second alkylation of the bicyclic lactams have been observed when straight-chain alkyl halides were used.[16] In spite of the low levels of diastereoselection, silica gel chromatography (ethyl acetate/hexane) provided good yields (65–80%) of the major

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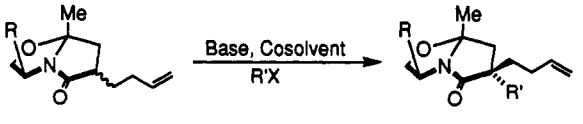
**Table II. Effect of Base and Cosolvent on Facial Selectivity of Alkylation of 13**



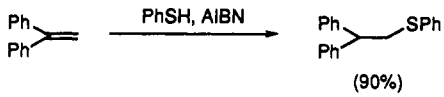

13 14

| R | base | cosolvent | R'X | *endo/exo*[a] |
|---|---|---|---|---|
| i-Pr | LDA | DMPU | BuBr | 2:1 |
| i-Pr | LDA | DMPU | EtBr | 1:1 |
| i-Pr | LDA | | EtBr | 2:1 |
| i-Pr | LiHMDS | | EtBr | *b* |
| t-Bu | LDA | | EtBr | 2:1 |
| t-Bu | LDA | | EtI | 3:1 |
| t-Bu | t-BuLi | | EtI | 3:1 |

[a] Determined by GC. [b] Enolization did not occur, and only starting material was recovered.

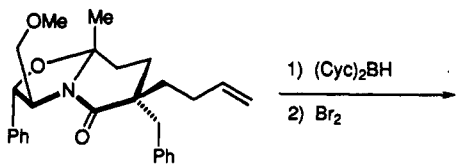
*endo*-alkylated lactams **14a–d**. The purified material was therefore coined through the synthetic sequence depicted in Scheme IV. Hydroboration–oxidation[17] of the terminal olefin followed by treatment with *N*-bromosuccinimide–triphenylphospine[18,19] provided the bromides **17a–c** which served as the sought after alkyllithium precursors.

Alternatively, preparation of the terminal alkyl phenyl sulfides **19** via an anti-Markownikoff addition[20] of thiophenol to the ω-olefins **18** was investigated. This one-step process of olefin elaboration initially seemed to be a potential improvement over the two-step elaboration to the terminal bromides **17a–c** since phenyl thioethers are readily converted to alkyllithiums when treated with lithium naphthalenide (LiNp).[20] The results reported in Table III show the olefin-containing bicyclic lactam to be extremely unreactive to the radical-initiated addition of benzenethiol. As an internal check of the thiolation process, 1,2-diphenylethylene was allowed to react with benzenethiol in the presence of 2,2′-azobisisobutyronitrile (AIBN) resulting in a 90% yield of the corresponding alkyl phenyl sulfide (eq 1).

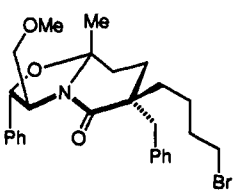



(90%) (1)

The one-pot conversion of the related 5,6-bicyclic lactam **20** to the terminal bromide **21** was also investigated (eq 2). Treatment of **20** with dicyclohexylborane (prepared



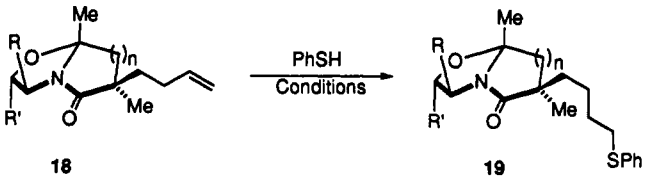

**20**




**21** (51%) (2)

*in situ* from cyclohexene and $BH_3$·THF) followed by addition of bromine[21] afforded **21** in 51% yield. Although this was promising, bromide **21**, obtained via the one-pot procedure, was exceedingly difficult to purify from the reaction mixture. As a result, the lengthier but more easily purified two-step hydroboration/bromination sequence was utilized in the final process.

**Table III. Anti-Markownikoff Addition of Benzenethiol to 18**




18 19

| entry | R | R′ | *n* | condns | result |
|---|---|---|---|---|---|
| a | i-Pr | H | 1 | AIBN, PhH, Δ | **19**, 43% |
| b | i-Pr | H | 1 | Ultrasound, PhH, Δ | NR |
| c | i-Pr | H | 1 | AIBN, Tol, Δ | 2.2:1 **19**:**18** |
| d | $CH_2OH$ | Ph[a] | 2 | AIBN, $CCl_4$, Δ | NR |
| e | $CH_2OH$ | Ph[a] | 2 | AIBN, PhH, Δ | NR |
| f | $CH_2OH$ | Ph[a] | 2 | AIBN, PhH, Δ, inverse addn | NR |
| g | $CH_2OH$ | Ph[a] | 2 | AIBN, neat, 85 °C, 2 d | 2.0:1 **18**:**19** |
| h | $CH_2OH$ | Ph[a] | 2 | hν, PhH | 2.7:1 **19**:**18** |
| i | $CH_2OH$ | Ph[a] | 2 | AIBN, neat, 85 °C, 5 d | **19**, 40% |

[a] Prepared from bicyclic lactam derived from 4-acetylbutyric acid + (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (Aldrich). See Experimental Section.

When the bromobutyl lactams **17a–c** were treated with *tert*-butyllithium in the presence of KH the halogen–metal exchange proceeded smoothly, providing the transient alkyllithium species **22a–c** which spontaneously cyclized to the carbinol amines **23a–c** (Scheme V). The ring-opened keto oxazolidines **24a–c** were also products of the halogen–metal exchange/cyclization reaction as evidenced by IR (1709 $cm^{-1}$).

The role of the KH in the halogen–metal exchange described above is uncertain. However, when KH was not added the isolated yields of the final hydrindenone products dropped markedly. Presumably, the KH acts as a proton scavenger which increases the yield of the cyclized carbinolamines **23a–c** at the expense of the proton quenched butyl lactams **26a–c**. The carbinolamines **23a–c** (and the correponding tautomereric keto oxazolidines **24a–c**) were subjected to hydrolysis (refluxing $Bu_4NH_2PO_{4(aq)}$) followed by aldol cyclization conditions (KOH–EtOH). The enantiomerically pure hydrindenones **4a–c** were isolated in 40–43% yield from lactams **17a–c**.

Stelliferin A, an isomalabaricane triterpene (**B**), was isolated from the Okinawan marine sponge *Jaspis stellifera* in 1991 and possesses potent antineoplastic activity.[9] The isomalabaricane skeleton is exceedingly rare, and the Stelliferins are only the second examples isolated from marine organisms. In order to access the tricyclic ring system with an eye toward preparing Stelliferin A in an enantioselective manner, the asymmetric synthesis of the related 3,3a,4,5-tetrahydro-3a-methyl-2*H*-benz[*e*]inden-2-ones **31a–c** was investigated (Scheme VI). Monoalkylated lactam **27a** was obtained via metalation–alkylation of **6** with LDA and 2-(2-bromophenyl)-1-iodoethane.[22] When 2-(2-bromophenyl)-1-bromoethane was utilized as the electrophile, recovery of a large amount of starting

(17) For a simple high-yielding preparation of 9-BBN dimer, see: Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 4599.

(18) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.

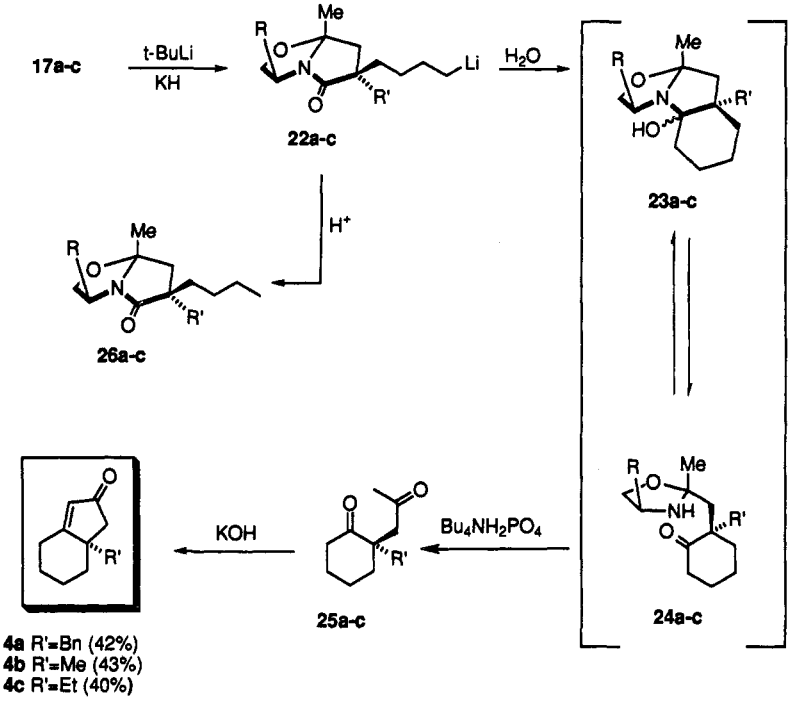
(19) Castro, B. R. *Org. React.* **1983**, *29*, 1.

(20) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064.

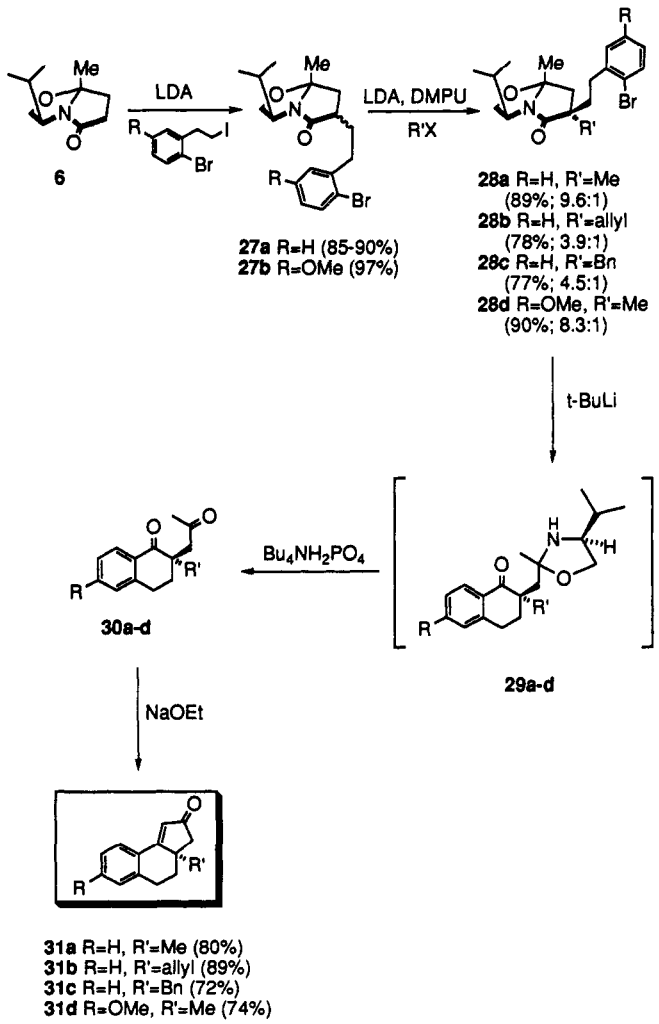
(21) Kabalka, G. W.; Sastry, K. A. R.; Hsu, H. C.; Hylarides, M. D. *J. Org. Chem.* **1981**, *46*, 3113.

(22) Wender, P. A.; White, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 2218.

**Scheme V**

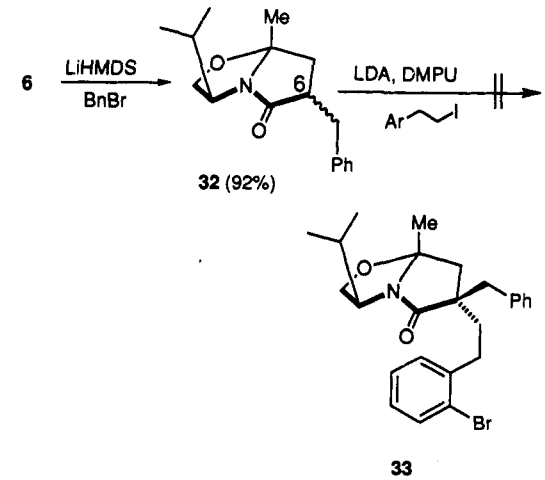



**Scheme VI**



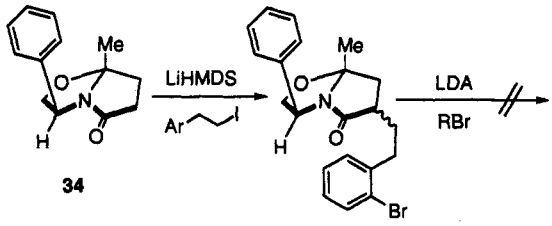

lactam **6** (typically greater than 50%) resulted, even after prolonged reaction times. Generation of the enolate of **27a** with LDA–DMPU followed by addition of an appropriate electrophile resulted in formation of lactams **28a–c** in excellent yields and good to moderate selectivity. The major diastereomers of **28a** and **28b** were purified via column or radial chromatography. In the case of **28c**, the $\Delta R_f$ was too small to affect complete separation of the major and minor diasteromers even after repeated radial chromatographies.

Since this study was not initially directed at preparing only one of the two possible benzindenone enantiomers, the order of introduction of the electrophiles was reversed in order to assess the diastereofacial selectivity of the bis-alkylation of lactam **32**. Enolization of lactam **6** with LiHMDS followed by alkylation with benzyl bromide provided the monoalkylated lactam **32** in 92% yield as a mixture of diastereomers at the 6-position (eq 3). The

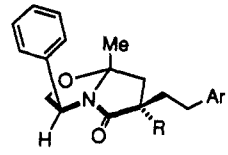



(3)

second alkylation (LDA–DMPU) with 2-(2-bromophenyl)-1-iodoethane proved ineffective as considerable amounts of starting lactam **32** were recovered. Changing the chiral auxiliary to the phenylglycinol-derived lactam **34**[11] was also ineffective as attempted enolization–alkylation of lactam **35** (prepared in 59% yield from **34**) resulted again in incomplete conversion to the bis-alkylated lactams **36** (eq 4). This is not very surprising as deprotonation of the kinetically accessible benzylic hydrogen would be expected



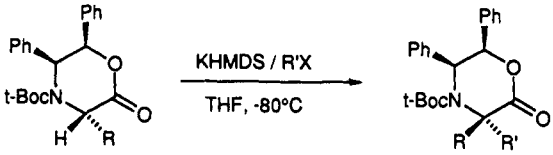

34 35 (59%)




36 (4)

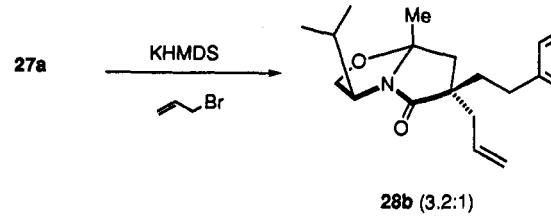
to compete with deprotonation of the sterically hindered tertiary proton.[23,24] Furthermore, changing the amide base to *sec*-butyllithium also failed as evidenced by TLC and GC analysis.

In a recent report, Williams *et al.*[25] reported the synthesis of α-substituted and α,α′-disubstituted amino acids via alkylation of chiral oxazinones followed by reductive removal of the chiral auxiliary. One of the interesting aspects of this study involved the discussion of the methods needed to effectively enolize the oxazinone lactone. It was found that in order to affect a clean, diastereoselective second alkylation it was necessary to treat a mixture of oxazinone and electrophile with potassium hexamethyldisilazide (KHMDS) as opposed to adding the electrophile to a preformed enolate (eq 5). The reason for this was




(5)

speculated to involve the nature of the preformed enolate, i.e., that it may exist as a dimer which inhibits smooth alkylation in a diastereoselective manner. By repeating these conditions with the bicyclic lactam **27a** and allyl bromide, complete conversion to the dialkylated lactam **28b** occurred in under 30 min at −78 °C, but unfortunately, the facial selectivity was no better than 3.2:1 (eq 6).




28b (3.2:1) (6)

With the dialkylated lactams **28a–c** in hand, treatment with t-BuLi (−78 °C, THF) affected conversion to the corresponding aryllithium species which cyclized within 30 min at −78 °C presumably to **29**. Quenching with tetrabutylammonium dihydrogen phospate buffer solution (1 M) and heating to reflux for ~6 h provided on workup the keto tetralones **30a–c** which were subjected to aldol cyclization conditions affording benz[*e*]inden-2-ones **31a–c** in excellent overall yields from lactams **28a–c** (72–89%).

In order to prepare the Stelliferin aliphatic A ring (**B**) it was envisioned that the installation of a methoxy group in the 7-position would allow for a regiocontrolled Birch reduction of the aromatic A ring, providing access to the functionalized Stelliferin A ring. In the event, alkylation of **6** with the requisite 2-(2-bromo-5-methoxyphenyl)-1-iodoethane[26] followed by a second diastereoselective alkylation with iodomethane, afforded the major *endo* adduct of bis-alkylated lactam **28d** in 87% overall yield and a diastereoselectivity of 8.3:1. The three-step procedure for benzindenone formation ((a) halogen–metal exchange, (b) hydrolysis, (c) aldol cyclization) provided the desired 3,3a,4,5-tetrahydro-7-methoxy-3a-methyl-2*H*-benz[*e*]-inden-2-one (**31d**)[27,28] in 74% yield from lactam **28d**. Further elaboration of **31d** could provide for an extremely simple and efficient asymmetric entry into the Stelliferin family of triterpenes.

In summary, novel and efficient asymmetric alkylations have been performed utilizing chiral nonracemic bicyclic lactams **6** and **15** allowing for the synthesis of optically active hydrindenones and benzindenones. The ABC ring system of the antineoplastic agent Stelliferin A has also been prepared in enantiomerically pure form. Further synthetic potential of the halogen–metal exchange protocol is currently being explored.

## Experimental Section

Microanalysis samples were prepared by recrystallization from ethyl acetate/hexanes or by microdistillation utilizing a sublimation apparatus (Aldrich) and were performed by Desert Analytics, Tuscon, AZ, and Atlantic Microlab, Inc., Norcross, GA. Melting points were obtained using a Mel-temp apparatus and are uncorrected.

Preparative flash column chromatography was performed on Amicon Matrex (20–45 μm) or Aldrich 951(58 μm) silica gel using a positive pressure of air. Thin-layer chromatography (TLC) was performed on aluminum-backed E. Merck 5554, 0.2-mm silica gel plates and visualized with vanillin in acidic ethanol, acidic ammonium molybdate, basic potassium permanganate, $I_2$ impregnated on silica gel, UV light, and/or ethanolic phosphomolybdic acid. Chromatotron plates were prepared utilizing EM Science silica gel 60 $PF_{254}$ containing gypsum. VPC analyses were performed on a crosslinked 10% SE-30 capillary column with a flow rate of 100 mL/min.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane, toluene, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU), triethylamine, and methanol were freshly distilled from $CaH_2$. Diisopropylamine was distilled from and stored over KOH. Ethyl acetate and hexanes were distilled prior to use. All alkyl halides were passed through a plug of neutral alumina prior to use. Alkyllithium reagents were obtained from Aldrich unless otherwise noted and were periodically titrated with 2,5-dimethoxybenzyl alcohol. All other reagents were obtained from Aldrich and were used without further purification unless otherwise noted.

**General Procedure A. Monoalkylation of Bicyclic Lactam 6[11] or 15.**[11] To a stirred solution of LDA (2.0 equiv; prepared from 2.0 equiv of diisopropylamine and 2.0 equiv of n-BuLi) in THF at −78 °C under argon was added the 5,5-bicyclic lactam in THF so that the final molarity of the reaction solution was ca. 0.1 M. After 1 h the electrophile (3.0 equiv; passed through a

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(25) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1992**, *113*, 9276.
(26) Prepared from 3-methoxyphenylacetic acid. For an approach to a similar electrophile, see: Collins, M. P.; Drew, M. G. B.; Mann, J.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3211.
(27) Packer, R. A.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 110.
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(29) Reference 26.

short plug of basic alumina immediately prior to use) was added neat, and after an additional 1 h at −78 °C, the reaction mixture was warmed to 0 °C for 2 h and quenched with $NH_4Cl$(sat). The biphasic mixture was diluted with ether, washed sequentially with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*.

**General Procedure B. Bis-alkylation of Monoalkylated 5,5-Bicyclic Lactams Obtained from General Procedure A.** To a stirred solution of LDA (1.5 equiv) in THF under argon at 0 °C was added DMPU (10% based on total volume of the reaction solution). The solution was cooled to −78 °C, and the 5,5-monoalkylated bicyclic lactam in THF was added (sufficient THF was used to provide ca. 0.1 M solution). After 2 h at −78 °C, the electrophile (2.0 equiv; passed through a short plug of basic alumina immediately prior to use) was added by slowly dripping down the side of the reaction flask (which was completely immersed in the cooling bath). The reaction progress was monitored by TLC (ethyl acetate/hexane/silica gel), and after completion (typically 1 h) it was warmed to 0 °C and quenched by addition of $NH_4Cl$(sat). The biphasic mixture was diluted with ether, washed sequentially with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*.

**Spiro Lactam 11.** Cyclization of lactam **9**, performed as described in general procedure B, afforded 24 mg (52%) of lactam **11** as a colorless oil after column chromatography (10% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 4.16 (dd, $J$ = 7.5, 8.5 Hz, 1H), 3.78 (dd, $J$ = 6.8, 8.6 Hz, 1H), 3.62–3.49 (m, 1H), 2.09 (s, 1H), 1.94–1.53 (m, 8H), 1.45 (s, 3H), 1.01 (d, $J$ = 6.7 Hz, 3H), 0.85 (d, $J$ = 6.6 Hz, 3H); IR (film) 2959, 2871, 1711, 1467, 1448, 1376, 1147 cm$^{-1}$; $^{13}$C NMR ($CDCl_3$) $\delta$ 183.90, 96.90, 70.72, 61.50, 54.10, 49.23, 39.45, 37.17, 33.94, 25.53, 25.48, 25.12, 20.57, 18.90.

**Bis-alkylated Lactam 8.** Bis-alkylation of lactam **7**, performed as described in general procedure B, afforded 14 mg (25%) of the major diastereomer of lactam **8** (*endo*) and 13 mg (24%) of the minor **10** (*exo*) after column chromatography (2% ethyl acetate/hexane). The remainder of the chromatography fractions were mixed and were discarded. Physical data for the major (*endo*) diastereomer are provided: $^1$H NMR ($CDCl_3$) $\delta$ 4.15 ( app t, $J$ = 8.2 Hz, 1H), 3.75 (dd, $J$ = 7.1, 8.7 Hz, 1H), 3.56–3.47 (m, 3H), 2.20 (d, $J$ = 13.6 Hz, 1H), 1.92 (d, $J$ = 13.6 Hz, 1H), 1.75–1.50 (m, 6H), 1.47 (s, 3H), 1.26 (s, 3H), 1.02 (d, $J$ = 6.7 Hz, 3H), 0.85 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 183.91, 96.73, 70.50, 61.74, 47.54, 46.04, 44.76, 37.51, 34.14, 32.88, 25.89, 21.79, 20.69, 18.93; IR (film) 2961, 2871, 1708, 1459, 1377, 1350, 1175, 1033 cm$^{-1}$.

**Bis-alkylated Lactam 14b.** Monoalkylation of lactam **6**, performed as described in general procedure A, afforded 4.13 g (91%) of monoalkylated lactam **13** (R = i-Pr) as a mixture of diastereomers after column chromatography (30% ethyl acetate/hexane).

Bis-alkylation, performed as described in general procedure B, afforded **14b** as a 6.9:1 mixture of *endo*/*exo* diasteromers. Column chromatography (10 → 20% ethyl acetate/hexane) provided 1.35 g (79%) of the major (*endo*) diastereomer as a colorless liquid. Physical data for the major diastereomer are provided: $^1$H NMR ($CDCl_3$) $\delta$ 5.79–5.73 (m, 1H), 5.04–4.92 (m, 2H), 4.16 (app t, $J$ = 8.3 Hz, 1H), 3.73 (app t, $J$ = 7.8 Hz, 1H), 3.62–3.52 (m, 1H), 2.15–2.01 (m, 4H), 1.66–1.56 (m, 3H), 1.45 (s, 3H), 1.14 (s, 3H), 1.02 (d, $J$ = 6.4 Hz, 3H), 0.85 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 184.50, 138.03, 114.77, 96.69, 70.24, 62.39, 47.10, 46.08, 38.87, 34.13, 29.10, 25.26, 24.73, 20.81, 18.92; IR (film) 2964, 1718, 1641, 1011 cm$^{-1}$; $[\alpha]_D$ = 26.1° ($c$ = 1.80, EtOH). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02. Found: C, 71.45; H, 9.97.

**Bis-alkylated Lactam 14a.** Bis-alkylation, performed as described in general procedure B, afforded **14a** as a 7.5:1 mixture of *endo*/*exo* diasteromers. Column chromatography (15% ethyl acetate/hexane) provided 2.51 g (91%) of lactam **14a** as an inseparable 7.5:1 *endo*/*exo* mixture of diastereomers: $^1$H NMR ($CDCl_3$) $\delta$ 7.29–7.12 ( m, 5H), 5.87–5.74 (m, 1H), 5.08–4.93 (m, 2H), 3.76–3.70 (m, 1H), 3.61–3.46 (m, 2H), 3.14–2.98 (m, 1H), 2.72–2.55 (m, 1H), 2.39 (d, $J$ = 13.5 Hz, 1H), 2.19–2.06 (m, 2H), 1.89–1.73 (m, 2H), 1.65–1.54 (m, 3H), 1.40 (s, 3H), 1.06–1.02 (m, 3H), 0.85–0.80 (m, 3H). No further characterization was obtained, and the diastereomeric mixture of *endo*-**14a** and *exo*-**14a** was carried directly on to the next step.

**Bis-alkylated Lactam 14d.** Monoalkylation of lactam **15**, performed as in general procedure A, afforded 735 mg (96%) of monoalkylated lactam as a mixture of diastereomers after column chromatography (20% ethyl acetate/hexane).

Bis-alkylation, performed as in general procedure B, afforded lactam **14d** as a 3:1 *endo*/*exo* diastereomeric mixture. Column chromatography (hexane → 10% ethyl acetate/hexane) provided 77 mg (65%) of the major (*endo*) diastereomer as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 5.81–5.72 (m, 1H), 5.02–4.90 (m, 2H), 4.05 (app t, $J$ = 8.6 Hz, 1H), 3.79 (app t, $J$ = 9.1 Hz, 1H), 3.65 (app t, $J$ = 8.3 Hz, 1H), 2.19 (d, $J$ = 14.0 Hz, 1H), 2.07–1.98 (m, 2H), 1.95 (d, $J$ = 14.0 Hz, 1H), 1.65–1.48 (m, 6H), 1.47 (s, 3H), 0.92 (s, 9H), 0.72 (app t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 185.7, 138.5, 115.0, 94.4, 67.3, 66.3, 51.7, 44.2, 37.9, 33.1, 29.6, 29.3, 27.6, 26.6, 8.9; IR (film) 2964, 1714, 1642, 1320, 1025, 910 cm$^{-1}$; $[\alpha]_D$ = +51.0° ($c$ 0.49, $CH_2Cl_2$). Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.13; H, 10.43; N, 4.94.

**General Procedure C. Hydroboration–Oxidation of Terminal Olefin Substrates 14a–d.** To a stirred solution of terminal olefin in THF (0.1 M) at 0 °C under argon was added 9-borabicyclo[3.3.1]nonane (9-BBN)[17] (3.0 equiv). After 12 h, the reaction mixture was quenched by the sequential addition of 3 M NaOH (3.6 equiv) and 30% $H_2O_2$ (13.5 equiv). The heterogeneous mixture was allowed to stir for 30 min, warmed to ambient temperature, and partitioned between dichloromethane and 10% NaOH. The aqueous layer was removed, and the organic layer was washed with brine, dried over $K_2CO_3$, and concentrated *in vacuo*.

**Hydroxy Lactam 16b.** Hydroboration/oxidation of olefin **14b**, performed as described in general procedure C, afforded 340 mg (83%) of alcohol **16b** as a colorless oil after column chromatography (75% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 4.18 (dd, $J$ = 7.9, 8.6 Hz, 1H), 3.75 (dd, $J$ = 7.1, 8.7Hz, 1H), 3.63–3.59 (m, 3H), 3.15 (br s, 1H), 2.15 (d, $J$ = 13.9 Hz, 1H), 2.04 (d, $J$ = 13.9 Hz, 1H), 1.75–1.27 (m, 7H), 1.48 (s, 3H), 1.15 (s, 3H), 1.03 (d, $J$ = 6.6 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H); $^{13}$C ($CDCl_3$) $\delta$ 184.71, 96.54, 69.94, 62.12, 61.81, 47.10, 45.67, 39.12, 33.80, 32.64, 24.97, 24.51, 20.76, 20.58, 18.66; IR (film) 3448, 2932, 1703, 1459, 1376, 1055 cm$^{-1}$; $[\alpha]_D$ = +22.5° ($c$ 0.80, EtOH).

**Hydroxy Lactam 16a.** Hydroboration/oxidation of olefin **14a** (7.5:1 *endo*/*exo* diastereomeric mixture), performed as described in general procedure C, afforded 1.17 g (74%) of alcohol **16a** as a colorless oil after column chromatography (60 → 75% ethyl acetate/hexane). An additional 191 mg (12%) of the C-6 epimeric product was isolated, arising from the minor diastereomer of **14a**. Physical data for the major diastereomer are provided: $^1$H NMR ($CDCl_3$) $\delta$ 7.28–7.12 (m, 5H), 3.79–3.47 (m, 6H), 3.00 (d, $J$ = 13.0 Hz, 1H), 2.70 (d, $J$ = 13.0 Hz, 1H), 2.40 (d, $J$ = 13.0 Hz, 1H), 1.88 (d, $J$ = 13.0 Hz, 1H), 1.79–1.42 (m, 7H), 1.39 (s, 3H), 1.04 (d, $J$ = 6.6 Hz, 3H, 0.84 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 183.65, 137.70, 130.55, 128.04, 126.45, 96.73, 69.91, 62.52, 52.72, 42.95, 41.71, 38.40, 33.98, 32.92, 25.54, 21.01, 20.86, 18.94; IR (film) 3600, 2936, 2871, 1705, 1378, 1031, 703 cm$^{-1}$; $[\alpha]_D$ = +73.4° ($c$ 0.56, $CH_2Cl_2$). Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04. Found: C, 72.93; H, 9.08.

**Hydroxy Lactam 16c.** Hydroboration/oxidation of olefin **14d**, performed as described in general procedure C, afforded 250 mg (85%) of alcohol **16c** as a colorless oil after column chromatography (75% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 3.98 (app t, $J$ = 8.7 Hz, 1H), 3.72 (app t, $J$ = 9.1 Hz, 1H), 3.59–3.47 (m, 3H), 2.73 (br s, 1H), 2.10 (d, $J$ = 14.0 Hz, 1H), 1.87 (d, $J$ = 14.0 Hz, 1H), 1.51–1.21 (m, 10H), 1.39 (s, 3H), 0.84 (s, 9H), 0.68 (app t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 185.6, 97.1, 66.9, 66.0, 62.1, 51.5, 43.9, 38.0, 32.9, 32.7, 29.2, 27.1, 26.2, 20.7, 8.4; IR (film) 3445, 2963, 1714, 1321, 1025 cm$^{-1}$; $[\alpha]_D$ = +55.5° ($c$ 0.45, $CH_2Cl_2$). Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.50; N, 4.71. Found: C, 68.43; H, 10.54; N, 4.61.

**General Procedure D. Conversion of Hydroxy Lactams 16a–c to Bromo Lactams 17a–c.**[18,19] To a stirred solution of the hydroxy lactam in dichloromethane (0.1 M) at 0 °C under argon was added triphenylphosphine (1.5 equiv) followed by *N*-bromosuccinimide (NBS) (1.5 equiv). After 1 h, water was added, and the reaction mixture was diluted with additional dichloromethane. The aqueous layer was removed, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*.

**Bromo Lactam 17b.** Alcohol **16b** was converted to bromide **17b** according to general procedure D affording 321 mg (75%) of **17b** as a colorless oil after column chromatography (30% ethyl acetate/hexane): $^1$H ($CDCl_3$) $\delta$ 4.19 (app t, $J$ = 8.0 Hz, 1H), 3.76 (dd, $J$ = 7.2, 8.3 Hz, 1H), 3.66–3.57 (m, 1H), 3.42 (app t, $J$ = 6.7 Hz, 2H), 2.13 (d, $J$ = 9.0 Hz, 1H), 2.05 (d, $J$ = 9.0 Hz, 1H), 1.92–1.81 (m, 2H), 1.70–1.40 (m, 5H), 1.49 (s, 3H), 1.16 (s, 3H), 1.05 (d, $J$ = 6.5 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H); $^{13}$C ($CDCl_3$) $\delta$ 184.57, 96.71, 70.22, 62.49, 47.13, 46.03, 38.65, 34.07, 33.26, 32.79, 25.29, 24.79, 23.37, 20.78, 18.91; IR (film) 2963, 2871, 1712, 1464, 1378, 1352 cm$^{-1}$; $[\alpha]_D$ = +11.13° ($c$ 0.97, $CH_2Cl_2$).

**Bromo Lactam 17a.** Alcohol **16a** was converted to bromide **17a** according to general procedure D affording 578 mg (74%) of **17a** as a colorless oil after column chromatography (20% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 7.29–7.12 (m, 5H), 3.73 (app t, $J$ = 8.0 Hz, 1H), 3.59–3.49 (m, 2H), 3.42 (dd, $J$ = 6.7, 7.5 Hz, 2H), 2.98 (d, $J$ = 13.3 Hz, 1H), 2.68 (d, $J$ = 13.3 Hz, 1H), 2.39 (d, $J$ = 14.3 Hz, 1H), 1.90–1.83 (m, 2H), 1.85 (d, $J$ = 14.3 Hz, 1H), 1.74–1.48 (m, 5H), 1.40 (s, 3H), 1.05 (d, $J$ = 6.6 Hz, 3H), 0.85 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 183.40, 137.58, 130.54, 128.07, 126.51, 96.69, 69.93, 62.55, 52.56, 42.99, 41.71, 37.68, 34.01, 33.41, 32.71, 25.48, 23.48, 20.85, 18.94; IR (film) 3030, 2958, 1706, 1455, 1377, 1032 cm$^{-1}$; $[\alpha]_D$ = +52.0° ($c$ 0.50, $CH_2Cl_2$). Anal. Calcd for $C_{21}H_{30}BrNO_2$: C, 61.76; H, 7.40. Found: C, 61.64; H, 7.35.

**Bromo Lactam 17c.** Alcohol **16c** was converted to bromide **17c** according to general procedure D affording 250 mg (87%) of **17c** as a colorless oil after column chromatography (30% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 4.06 (app t, $J$ = 8.5 Hz, 1H), 3.80 (app t, $J$ = 9.1 Hz, 1H), 3.66 (app t, $J$ = 9.1 Hz, 1H), 3.38 (app t, $J$ = 6.67 Hz, 2H), 2.20 (d, $J$ = 14.1 Hz, 1H), 1.95 (d, $J$ = 14.1 Hz, 1H), 1.89–1.78 (m, 2H), 1.60–1.39 (m, 6H), 1.48 (s, 3H), 0.93 (s, 9H), 0.77 (app t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 185.5, 97.1, 66.9, 65.9, 51.4, 43.8, 37.3, 33.4, 32.8, 29.3, 27.2, 26.3, 23.2, 8.6; IR (film) 2964, 1712, 1462, 1376, 1320, 1232, 1025 cm$^{-1}$; $[\alpha]_D$ = +37.8° ($c$ 0.45, $CH_2Cl_2$). Anal. Calcd for $C_{17}H_{30}NO_2Br$: C, 56.66; H, 8.39; N, 3.89. Found: C, 56.69; H, 8.38; N, 3.83.

**General Procedure E. Preparation of 7a-Alkyl-2,4,6,7,7a-hexahydro-1*H*-inden-2-ones 4a–c from Bromo Lactams 17a–c.** To a stirred solution of bromolactam in THF (0.05 M) under argon at –78 °C was added KH (3.0 equiv) followed by t-BuLi (2.1 equiv). After 45 min, the mixture was quenched with water, and the THF was removed *in vacuo*. To the remaining aqueous product was added absolute ethanol (sufficient quantity to dissolve the heterogeneous mixture) and 1 M $Bu_4NH_2PO_4$ solution (30 equiv). The mixture was heated to reflux for 12 h, the reflux condensor was removed, and the solution was concentrated to ca. one-third its original volume. The resultant solution was allowed to cool to ambient temperature, diluted with brine, and extracted with ether. The organic layer was removed, and the aqueous layer was reextracted with three portions of ether. The combined organics were dried over $MgSO_4$ and concentrated at atmospheric pressure to ca. 10 mL. Ethanolic KOH (1 M) was added, and after 16 h, brine was added, the aqueous solution was extracted with three portions of ether, and the combined organics were dried over $MgSO_4$ and concentrated at atmospheric pressure to near-dryness.

**Hydrindenone 4b.** Terminal bromide **17b** was converted to hydrindenone **4b**[7] according to general procedure E affording 63 mg (43%) of **4b** as a colorless oil after column chromatography (30% ethyl acetate/hexane): $^1$H ($CDCl_3$) $\delta$ 5.77 (s, 1H), 2.69–2.61 (m, 1H), 2.46–1.91 (m, 5H), 1.79–1.66 (m, 2H), 1.49–1.33 (m, 2H), 1.26 (s, 3H); $^{13}$C ($CDCl_3$) $\delta$ 208.00, 188.30, 126.14, 52.25, 43.12, 40.74, 27.91, 27.86, 24.09, 21.88; IR (film) 2932, 2862, 1714, 1622, 1221 cm$^{-1}$; $[\alpha]_D$ = +9.15° ($c$ 0.59, EtOH); GC/MS $m/z$ (abundance), 151 ($M^+$ + 1), 150 ($M^+$), 135 ($M^+$ – 15).

**Hydrindenone 4a.** Terminal bromide **17a** was converted to hydrindenone **4a** according to general procedure E affording 87 mg (42%) of **4a** as a colorless oil after column chromatography (30 → 40% ethyl acetate/hexane with 10 drops of triethylamine per 200 mL mobile phase): $^1$H NMR ($CDCl_3$) $\delta$ 7.27–7.19 (m, 3H), 7.08–7.05 (m, 2H), 5.78 (s, 1H), 2.95–2.52 (m, 5H), 2.14–1.69 (m, 5H), 1.50–1.32 (m, 2H); $^{13}$C ($CDCl_3$) $\delta$ 207.19, 189.21, 137.21, 129.93, 128.05, 127.81, 126.50, 48.22, 47.49, 40.75, 39.04, 28.23, 27.90, 21.59; IR (film) 3061, 3028, 2933, 2858, 1704, 1621, 1495, 1454, 760, 702 cm$^{-1}$; $[\alpha]_D$ = +20.4° ($c$ 0.74, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.68; H, 8.08.

**Hydrindenone 4c.** Terminal bromide **17c** was converted to hydrindenone **4c** according to general procedure E affording 52 mg (40%) of **4c** as a colorless oil after column chromatography (30% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 5.77 (d, $J$ = 1.3 Hz, 1H), 2.65–2.52 (m, 1H), 2.36–2.18 (m, 2H), 2.07–1.83 (m, 4H), 1.77–1.48 (m, 5H), 1.45–1.20 (m, 2H), 0.71 (app t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.1, 187.3, 127.3, 48.9, 46.8, 38.6, 28.1, 27.6, 27.4, 21.4, 8.3; IR (film) 2962, 1710, 1622, 1458, 1217 cm$^{-1}$; $[\alpha]_D$ = +44.8° ($c$ 0.67, $CH_2Cl_2$); GC/MS $m/z$ (abundance), 165 ($M^+$ + 1), 164 ($M^+$), 149 ($M^+$ – 15), 135 ($M^+$ – 29).

**(Phenylthio)alkyl Lactam 19a.** To 47 mg (0.19 mmol) of lactam **14b** in 1 mL of benzene was added 38 μL (0.37 mmol) of benzenethiol followed by a spatula tip of AIBN. The mixture was heated to reflux overnight, diluted with 15 mL of benzene, washed with 3 × 5 mL of 10% NaOH, 5 mL of $H_2O$, and 5 mL of brine, and dried over $MgSO_4$. The solution was concentrated *in vacuo* to 127 mg of yellow oil which was judged to be 1:1 product/starting material by $^1$H NMR. Column chromatography (10 → 15% ethyl acetate/hexane) afforded 30 mg (43%) of **19a** as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.31–7.14 (m, 5H), 4.18–4.08 (m, 1H), 3.73 (app t, $J$ = 7.8 Hz, 1H), 3.61–3.50 (m, 1H), 2.90 (app t, $J$ = 7.3 Hz, 2H), 2.11–1.99 (m, 2H), 1.68–1.45 (m, 6H), 1.43 (s, 3H), 1.28–1.18 (m, 1H), 1.12 (s, 3H), 1.02 (d, $J$ = 6.5 Hz, 3H), 0.85 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 184.67, 136.62, 129.07, 128.83, 125.81, 96.71, 70.24, 62.37, 47.21, 45.94, 39.15, 34.13, 33.38, 29.39, 25.24, 24.80, 23.91, 20.87, 18.91; IR (film) 2958, 2935, 1712, 1460, 1374 cm$^{-1}$.

**Bis-alkylated Lactam 18d.** To a stirred solution of 6.45 mL (46.1 mmol) of diisopropylamine in 150 mL of THF under argon at 0 °C was added dropwise 30.7 mL (46.1 mmol) of n-BuLi. After being stirred for 20 min at 0 °C, the solution was cooled to –78 °C, and 4.01 g (15.4 mmol) of (2*S*,3*S*,8a*R*)-hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5-oxo-5*H*-oxazolo[3,2-*a*]pyridine (5,6-bicyclic lactam)[30] in 50 mL of THF was added via syringe. The solution was immediately warmed to 0 °C for 1.25 h and cooled to –78 °C, and 4.70 mL (46.1 mmol) of 4-bromo-1-butene was added neat. After being stirred for 15 min at –78 °C, the solution was warmed to 0 °C for 2 h and stored in a 0 °C freezer overnight. The reaction was quenched with 50 mL of 1 N HCl and concentrated *in vacuo* to remove the THF. The acidic aqueous layer was extracted with 3 × 75 mL of dichloromethane, and the combined organics were then washed with 50 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to 4.50 g of yellow oil. Column chromatography (80 → 95% ethyl acetate/hexane) provided 2.09 g (89% based on consumed starting material) of monoalkylated lactam as a mixture of diastereomers which was used directly in the next step.

To a stirred solution of 3.30 mL (23.9 mmol) of diisopropylamine in 50 mL of THF under argon at 0 °C was added 15.9 mL (23.9 mmol) of n-BuLi. After being stirred at 0 °C for 15 min, 10 mL of DMPU was added, the solution was cooled to –78 °C, and 2.08 g (7.97 mmol) of monoalkylated lactam prepared above in 20 mL of THF was added via cannula. The reaction was warmed to 0 °C for 3.5 h and cooled to –90 °C, and 1.49 mL (23.9 mmol) of iodomethane was added neat down the side of the flask. After being stirred for 20 min, the reaction was warmed to –78 °C and stirred overnight, quenched with 20 mL of 1 N HCl, and concentrated *in vacuo* to remove the THF. The aqueous layer was extracted with 4 × 25 mL of diethyl ether, the combined organics were washed with 2 × 25 mL of $H_2O$, 20 mL of 1 M $Na_2S_2O_5$, and 25 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to 3.14 g of yellow liquid. Column chromatography (60% ethyl acetate/hexane) provided 1.81 g of white solid which was recrystallized from ethyl acetate/hexane to provide 1.18 g (49%) of pure **18d**: mp 168–169 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.35 (s, 5H), 5.85–5.75 (m, 1H), 5.07–4.94 (m, 3H), 4.77 (d, $J$ = 8.5 Hz, 1H), 4.07 (app dt, $J$ = 2.4, 8.6 Hz, 1H), 3.91–3.83 (m, 1H), 3.76–3.68 (m, 1H), 2.15–1.84 (m, 7H), 1.71–1.58 (m, 1H), 1.56 (s, 3H), 1.26 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.93, 137.93, 137.83, 128.60, 126.48, 114.71, 93.80, 78.33, 66.83, 64.95, 41.46, 39.41, 32.44, 29.24, 28.67, 26.26, 24.24; IR (DMSO) 3443, 1635 cm$^{-1}$; $[\alpha]_D$ = –8.84 ($c$ = 1.2, EtOH). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26. Found: C, 72.82; H, 8.17.

**Lactam 20.** To a stirred solution of 12.9 mL (91.9 mmol) of diisopropylamine in 425 mL of THF under argon at 0 °C was

(30) Meyers, A. I.; Berney, D. *Org. Synth.* **1990**, *69*, 55.

added dropwise 61.0 mL (91.9 mmol) of n-BuLi. After the solution was stirred for 20 min at 0 °C, 50 mL (10% v/v) of DMPU was added, the solution was cooled to −78 °C, and 8.0 g (30.7 mmol) of (2*S*,3*S*,8a*R*)-hexahydro-3-hydroxymethyl-8a-methyl-2-phenyl-5-oxo-5*H*-oxazolo[3,2-*a*]pyridine (5,6-bicyclic lactam)[30] in 50 mL of THF was added via syringe. The solution was immediately warmed to 0 °C for 1.25 h and cooled to −78 °C, and 12.4 mL (122.6 mmol) of 4-bromo-1-butene was added neat. After being stirred for 15 min at −78 °C, the solution was warmed to 0 °C for 2 h and stored in a 0 °C freezer overnight. The reaction was quenched with 50 mL of 1 N HCl and concentrated *in vacuo* to remove the THF. The acidic aqueous layer was extracted with 3 × 75 mL of dichloromethane, and the combined organics were then washed with 50 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to 4.50 g of yellow oil. Column chromatography (80 → 95% ethyl acetate/hexane) provided 4.05 g (83% based on consumed starting material) of monoalkylated lactam as a mixture of diastereomers which was used directly in the next step.

To a stirred solution of 5.2 mL (36.8 mmol) of diisopropylamine in 150 mL of THF under argon at 0 °C was added 24.6 mL (36.8 mmol) of n-BuLi. After the solution was stirred at 0 °C for 15 min, 20 mL (10% v/v) of DMPU was added, the solution was cooled to −78 °C, and 3.9 g (12.3 mmol) of monoalkylated lactam prepared above in 50 mL of THF was added via cannula. The reaction was warmed to 0 °C for 3.5 h and cooled to −90 °C, and 4.4 mL (36.8 mmol) of benzyl bromide was added neat down the side of the flask. After being stirred for 20 min, the reaction was warmed to −78 °C and stirred overnight, quenched with 20 mL of 1 N HCl, and concentrated *in vacuo* to remove the THF. The aqueous layer was extracted with 4 × 25 mL of diethyl ether, the combined organics were washed with 2 × 25 mL of $H_2O$, 20 mL of 1 M $Na_2S_2O_3$, and 25 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to 3.14 g of yellow liquid. Column chromatography (60% ethyl acetate/hexane) provided 3.19 g (64%) white solid consisting of a 7.3:1 *endo/exo* diastereomeric ratio. Recrystallization from ethyl acetate/hexane provided 2.5 g (49%) of pure bis-alkylated lactam: mp 141–142 °C; $^1$H NMR ($CDCl_3$) δ 7.37–7.18 (m, 10H), 5.95–5.78 (m, 1H), 5.28 (dd, *J* = 1.4, 8.0 Hz, 1H), 5.10–4.98 (m, 2H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.06–4.02 (m, 1H), 3.88–3.85 (m, 1H), 3.78–3.74 (m, 1H), 3.39 (d, *J* = 12.9 Hz, 1H), 2.57 (d, *J* = 12.9 Hz, 1H), 2.25–1.54 (m, 8H), 1.47 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 175.00, 138.06, 137.82, 129.83, 128.84, 128.68, 128.58, 126.92, 126.71, 115.10, 93.87, 78.48, 77.42, 77.00, 76.58, 67.55, 65.34, 47.03, 46.23, 40.34, 32.73, 28,76, 26.75, 24.52; IR (film) 3316, 3062, 3030, 2943, 1641, 1085, 1054 cm$^{-1}$; $[\alpha]_D$ = 106.5 (*c* = 1.35, EtOH). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.71. Found: C, 77.09; H, 7.61.

To 2.26 g (5.58 mmol) of bis-alkylated lactam prepared above in 50 mL of THF at 0 °C under argon was added 201 mg (8.37 mmol) of NaH followed by 0.50 mL (8.03 mmol) of iodomethane. The reaction mixture was allowed to warm to ambient temperature and quenched after 3 h with saturated $NH_4Cl$. The THF was removed *in vacuo*, and the resultant aqueous solution was extracted with dichloromethane, dried over $MgSO_4$, and concentrated *in vacuo* to 2.33 g (100%) of lactam **20**: $^1$H NMR ($CDCl_3$) δ 7.35–7.18 (m, 10H), 5.91–5.78 (m, 1H), 5.15 (d, *J* = 7.8 Hz, 1H), 5.08–4.96 (m, 2H), 4.11–4.06 (m, 1H), 3.82–3.76 (m, 1H), 3.69–3.65 (m, 1H), 3.43–3.37 (m, 4H), 2.53 (d, *J* = 12.9 Hz, 1H), 2.01–1.59 (m, 8H), 1.51 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 172.76, 139.62, 138.47, 138.18, 130.03, 128.43, 128.38, 128.20, 126.69, 114.80, 93.47, 78.66, 70.68, 63.80, 59.24, 46.58, 46.42, 40.48, 32.94, 28.78, 26.50, 24.15; IR (film) 3063, 3029, 2938, 1637, 1028 cm$^{-1}$.

**Bromo Lactam 21.** To a stirred solution of 1.98 mL (1.98 mmol) of $BH_3$-THF in 10 mL of THF under argon at 0 °C was added 0.41 mL (4.06 mmol) of cyclohexene. The resulting heterogeneous mixture was stirred at 0 °C for 2 h, and 792 mg (1.89 mmol) of lactam **20** in 10 mL of THF was added via cannula. After an additional 15 min at 0 °C the solution was warmed to ambient temperature for 1 h and cooled to 0 °C, the reaction vessel was covered with aluminum foil, and 1.89 mL (1.89 mmol) of 1 M $Br_2/CCl_4$ was added. After 1 h, 50 mL of ether was added, and the organic phase was washed with 2 × 10 mL of $H_2O$ and 10 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo* to 1.26 g of oil. Column chromatography (10 → 20% ethyl acetate/hexane) provided 486 mg (51%) **21** as a white powder: $^1$H NMR ($CDCl_3$) δ 7.37–7.18 (m, 10H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.14–4.04 (m, 1H), 3.79 (dd, *J* = 5.5, 10.2 Hz, 1H), 3.66 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.43–3.41 (m, 1H), 3.37 (s, 3H), 2.50 ( d, *J* = 12.9 Hz, 1H), 1.92–1.69 ( m, 6H), 1.51 (s, 3H), 1.44–1.25 (m, 3H), 0.96–0.82 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 172.76, 139.55, 138.39, 129.94, 128.40, 128.36, 128.17, 126.65, 93.45, 78.53, 77.43, 77.00, 76.58, 70.49, 63.82, 59.25, 46.62, 40.16, 33.72, 32.88, 32.65, 26.50, 24.06, 22.97; IR (film) 3060, 3029, 2940, 1634, 1026 cm$^{-1}$; $[\alpha]_D$ = 88.5° (*c* = 1.0, EtOH); mp 68–70 °C. Anal. Calcd for $C_{27}H_{34}BrNO_3$: C, 64.80; H, 6.85. Found: C, 64.71; H, 6.86.

**Monoalkylated Lactam 27a.** Monoalkylation of lactam **6** was performed as described in general procedure A utilizing 2-(2-bromophenyl)-1-iodoethane[22] as electrophile and provided 1.91 g (95%) of lactam **27a** (mixture of *endo* and *exo* diastereomers) as a yellow liquid after column chromatography (10% ethyl acetate/hexane). Physical data for the major (*endo*) diastereomer are provided: $^1$H NMR ($CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.27–7.18 (m, 2H), 7.07–7.01 (m, 1H), 4.17 (app t, *J* = 8.1 Hz, 1H), 3.76 (dd, *J* = 6.9, 8.7 Hz, 1H), 3.63–3.54 (m, 1H), 2.86–2.80 (m, 2H), 2.65–2.58 (m, 1H), 2.43 (dd, *J* = 10.2, 13.9 Hz, 1H), 2.12–2.02 (m, 1H), 1.96 (dd, *J* = 3.8, 13.9 Hz, 1H), 1.90–1.79 (m, 1H), 1.68–1.58 (m, 1H), 1.49 (s, 3H), 1.03 (d, 6.6 Hz, 3H), 0.86 (d, 6.6 Hz, 3H). No further characterization was obtained, and the diastereomeric mixture was carried on to the next step.

**Bis-alkylated Lactam 28a.** Bis-alkylation of lactam **27a**, performed as described in general procedure B, afforded a 79% yield of a 9.6:1 *endo/exo* ratio of lactam **28a**. Column chromatography (2 → 5% ethyl acetate/hexane) provided 171 mg (68%) of the major (*endo*) and 26 mg (10%) of the minor (*exo*) diastereomers. Physical data for the major diastereomer are provided: $^1$H NMR ($CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.28–7.17 (m, 2H), 7.09–7.01 (m, 1H), 4.19 (app t, *J* = 8.1 Hz, 1H), 3.78 (dd, *J* = 6.9, 8.5 Hz, 1H), 3.68–3.56 (m, 1H), 2.85–2.63 (m, 2H), 2.29 (d, *J* = 13.9 Hz, 1H), 2.11 (d, *J* = 13.9 Hz, 1H), 1.90–1.75 (m, 2H), 1.69–1.55 (m, 1H), 1.51 (s, 3H), 1.23 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 183.92, 140.98, 132.79, 130.36, 127.76, 127.63, 124.19, 96.71, 70.40, 62.12, 47.45, 46.38, 40.05, 34.17, 31.87, 25.33, 24.15, 20.80, 18.93; IR (film) 3062, 2960, 1708 cm$^{-1}$; $[\alpha]_D$ = +2.7° (*c* 1.09, $CH_2Cl_2$). Anal. Calcd for $C_{19}H_{26}BrNO_2$: C, 60.00; H, 6.89. Found: C, 60.02; H, 6.90.

**Bis-alkylated Lactam 28b.** Bis-alkylation of lactam **27a**, performed as described in general procedure B, afforded a 78% yield of a 3.9:1 *endo/exo* ratio of lactam **28b**. Radial chromatography (1 → 5% ethyl acetate/hexane; 2 mm) provided 151 mg (60%) of the major (*endo*) diastereomer as a pale yellow oil: $^1$H NMR ($CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 1H), 7.24–7.16 (m, 2H), 7.06–7.00 (m, 1H), 5.76–5.62 (m, 1H), 5.13–5.07 (m, 2H), 4.16 (app t, *J* = 8.1 Hz, 1H), 3.75 (dd, *J* = 7.0, 8.6 Hz, 1H), 3.65–3.56 (m, 1H), 2.85–2.63 (m, 2H), 2.36–2.28 (m, 3H), 2.08 (d, *J* = 14.1 Hz, 1H), 1.87–1.79 (m, 2H), 1.67–1.55 (m, 1H), 1.51 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 183.04, 141.30, 134.06, 133.12, 130.72, 128.12, 127.99, 124.53, 119.06, 97.24, 70.67, 62.37, 51.42, 43.45, 41.42, 38.93, 34.51, 32.04, 25.81, 21.18, 19.28; IR (film) 3075, 2960, 1708 cm$^{-1}$; $[\alpha]_D$ = +22.0° (*c* 0.65, $CH_2Cl_2$). Anal. Calcd for $C_{21}H_{28}BrNO_2$: C, 62.07; H, 6.94. Found: C, 62.37; H, 6.93.

**Bis-alkylated Lactam 28c.** Bis-alkylation of lactam **27a**, performed as described in general procedure B, afforded a 77% yield of a 4.5:1 *endo/exo* ratio of lactam **28c**. Repeated radial chromatography (5% ethyl acetate/hexane; 2 mm) provided only partial separation of the major and minor diastereomers and afforded 74 mg (35%) of lactam **28c** as a colorless oil: $^1$H NMR ($CDCl_3$) δ 7.49 (d, 7.9 Hz, 1H), 7.27–7.15 (m, 7H), 7.07–7.01 (m, 1H), 3.76–3.70 (m, 1H), 3.60–3.52 (m, 2H), 3.08 (d, 13.4 Hz, 1H), 2.88–2.69 (m, 2H), 2.73 (d, *J* = 13.4 Hz, 1H), 2.42 (d, *J* = 14.3 Hz, 1H), 2.02 (d, *J* = 14.2 Hz, 1H), 1.94–1.82 (m, 2H), 1.63–1.56 (m, 1H), 1.44 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 182.87, 140.89, 137.54, 132.78, 130.52, 130.35, 128.08, 127.79, 127.64, 126.50, 124.23, 96.71, 69.99, 62.34, 52.79, 42.49, 42.00, 39.06, 34.01, 31.86, 25.51, 20.82, 18.96; IR (film) 3060, 3031, 2959, 1706, 749, 703 cm$^{-1}$; $[\alpha]_D$ = +31.4° (*c* 0.22, $CH_2Cl_2$). Anal. Calcd for $C_{25}H_{30}BrNO_2$: C, 65.79; H, 6.63. Found: C, 65.50; H, 6.64.

**General Procedure F. Preparation of 3,3a,4,5-Tetrahydro-7-methoxy-3a-alkyl-2*H*-benz[*e*]inden-2-ones 31a–d from Bromophenyl Lactams 28a–d.** To a stirred solution of bromophenyl lactam in THF (0.5 M) under argon at −78 °C was added t-BuLi (2.1 equiv) resulting in a bright yellow solution

which was quenched by the addition of 1 M n-$Bu_4NH_2PO_4$ buffer (30 equiv) after 1 h. The THF was removed *in vacuo*, and the resultant aqueous solution was refluxed for 12 h, cooled to ambient temperature, and extracted with three portions of 1:1 ether/pentane. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a colorless oil which was dissolved in THF (0.5 M), treated with 1 M NaOEt/EtOH (1.0 equiv), and heated to reflux for 24 h. The reaction mixture was allowed to cool to ambient temperature, diluted with water, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*.

**Benzindenone 31a.** Bromophenyl lactam **28a** was converted to benzindenone **31a** as described in general procedure F affording 41 mg (79%) of **31a** as a pale yellow solid after column chromatography (15% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 7.61–7.59 (m, 1H), 7.37–7.32 (m, 1H), 7.28–7.20 (m, 2H), 6.26 (s, 1H), 3.14–3.11 (m, 1H), 2.91 (dd, $J$ = 5.0, 17.3 Hz, 1H), 2.48 (d, $J$ = 18.1 Hz, 1H), 2.34 (d, $J$ = 18.1 Hz, 1H), 2.09–2.03 (m, 1H), 1.85 (app dt, $J$ = 6.1, 13.0 Hz, 1H), 1.21 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.49, 179.14, 137.78, 130.89, 129.57, 129.21, 127.43, 126.53, 122.62, 52.10, 41.03, 34.55, 26.29, 24.58; IR (film) 3062, 2924, 1692, 1599 cm$^{-1}$; $[\alpha]_D$ = −287.7° (*c* 0.65, $CH_2Cl_2$); mp 55–57 °C. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.66; H, 7.17.

**Benzindenone 31b.** Bromophenyl lactam **28b** was converted to benzindenone **31b** as described in general procedure F affording 45 mg (89%) of **31b** as a pale yellow oil after column chromatography (15% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 7.61–7.58 (m, 1H), 7.38–7.33 (m, 1H), 7.28–7.21 (m, 2H), 6.29 (s, 1H), 5.76–5.62 (m, 1H), 5.10–5.00 (m, 2H), 3.12–3.00 (m, 1H), 2.88 (dd, $J$ = 5.2, 17.5Hz, 1H), 2.63 (d, $J$ = 18.0 Hz, 1H), 2.32 (dd, $J$ = 8.2, 13.9 Hz, 1H), 2.22–2.05 (m, 1H), 2.17 (d, $J$ = 18.0 Hz, 1H), 1.83 (app dt, $J$ = 6.1, 12.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.19, 177.78, 137.73, 133.31, 130.95, 129.61, 129.28, 127.41, 126.64, 123.71, 118.96, 48.70, 44.17, 40.07, 32.31, 25.76; IR (film) 3073, 2921, 1700, 1600 cm$^{-1}$; $[\alpha]_D$ = −251.4° (*c* 1.40, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.58; H, 7.23.

**Benzindenone 31c.** Bromophenyl lactam **28c** was converted to benzindenone **31c** as described in general procedure F affording 13.6 mg (72%) of **31c** as a white solid after column chromatography (15% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (d, $J$ = 7.7 Hz, 1H), 7.43–7.18 (m, 6H), 6.99–6.96 (m, 2H), 6.20 (s, 1H), 3.35–3.23 (m, 1H), 2.99 (dd, $J$ = 6.0, 18.2 Hz, 1H), 2.80 (s, 2H), 2.73 (d, $J$ = 18.1 Hz, 1H), 2.24 (dd, $J$ = 5.2, 13.4 Hz, 1H), 2.11 (d, $J$ = 18.0 Hz, 1H), 1.94 (app dt, $J$ = 6.2, 13.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 206.56, 176.98, 137.45, 136.71, 130.96, 130.31, 129.70, 128.09, 127.36, 126.84, 126.67, 124.68, 48.37, 45.29, 41.22, 33.44, 26.08; IR (film) 3062, 3030, 2921, 1700, 1600, 754, 700; $[\alpha]_D$ = −183.6° (*c* 1.34, $CH_2Cl_2$); mp 126–127 °C. Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.61; H, 6.63.

**Bis-alkylated Lactam 28d.** Monoalkylation of lactam **6**, performed as described in general procedure A, utilizing 2-(2-bromo-5-methoxyphenyl)-1-iodoethane as electrophile, provided 1.05 g (97%) of lactam **27b** (mixture of *endo* and *exo* diastereomers) as an amber liquid after column chromatography (20% ethyl acetate/hexane) which was used without any further purification in the next step.

Bis-alkylation of lactam **27b**, performed as described in general procedure B, afforded a 90% yield of a 8.3:1 *endo*/*exo* ratio of lactam **28d**. Column chromatography (5 → 10% ethyl acetate/hexane) provided 367 mg (80%) of the major (*endo*) and 44 mg (10%) of the minor (*exo*) diastereomers. Physical data for the major diastereomer are provided: $^1$H NMR ($CDCl_3$) $\delta$ 7.24 (d, $J$ = 8.8 Hz, 1H), 6.72 (d, $J$ = 3.0 Hz, 1H), 6.61 (dd, $J$ = 3.0, 8.7 Hz, 1H), 4.18 (app t, $J$ = 8.2 Hz, 1H), 3.73 (s, 3H), 3.77–3.72 (m, 1H), 3.63–3.55 (m, 1H), 2.73–2.62 (m, 2H), 2.27 (d, $J$ = 13.9 Hz, 1H), 2.08 (d, $J$ = 14.0 Hz, 1H), 1.83–1.75 (m, 2H), 1.66–1.53 (m, 1H), 1.50 (s, 3H), 1.22 (s, 3H), 1.03 (d, $J$ = 6.6 Hz, 3H), 0.85 (s, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 183.92, 159.04, 141.89, 133.23, 115.77, 114.53, 113.50, 96.68, 70.31, 62.11, 55.37, 47.37, 46.29, 39.96, 34.12, 32.08, 25.27, 24.17, 20.76, 18.89; IR (film) 3063, 2962, 1709 cm$^{-1}$; $[\alpha]_D$ = +5.7° (*c* 0.87, $CH_2Cl_2$). Anal. Calcd for $C_{20}H_{28}BrNO_3$: C, 58.54; H, 6.88. Found: C, 58.60; H, 6.93.

**Methoxybenzindenone 31d.** Bromophenyl lactam **28d** was converted to benzindenone **31d** as described in general procedure F, affording 53 mg (74%) of **31d** as a yellow solid after column chromatography (15% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$) $\delta$ 7.54 (d, $J$ = 8.6 Hz, 1H), 6.80 (dd, $J$ = 2.5, 8.7 Hz, 1H), 6.71 (d, $J$ = 2.5 Hz, 1H), 6.14 (s, 1H), 3.82 (s, 3H), 3.11–2.99 (m, 1H), 2.86 (dd, $J$ = 5.4, 17.6 Hz, 1H), 2.44 (d, $J$ = 17.7 Hz, 1H), 2.33 (d, $J$ = 17.7 Hz, 1H), 2.02 (dd, $J$ = 5.5, 13.1 Hz, 1H), 1.83 (app dt, $J$ = 5.8, 12.7 Hz, 1H), 1.20 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.25, 179.05, 161.71, 139.96, 129.28, 122.30, 120.72, 113.57, 113.46, 55.34, 52.03, 41.10, 34.41, 26.74, 24.89; IR (film) 3063, 2926, 1690, 1592, 1266 cm$^{-1}$; $[\alpha]_D$ = −402.6° (*c* 0.39, $CH_2Cl_2$); mp 113–115 °C (lit.[28] racemate mp 94–95 °C).

**3-Methoxyphenethyl Alcohol.** To 6.25 g (0.16 mol) of $NaBH_4$ in 600 mL of THF was added 22.75 g (0.14 mol) of 3-methoxyphenylacetic acid over 10 min followed by $I_2$ in 125 mL of THF over 1.5 h. The reaction vessel was fitted with a $CaSO_4$ drying tube, allowed to stir for 16 h, and quenched by the careful addition of sufficient 1 M HCl to provide a clear solution. The aqueous solution was extracted with ether, and the organic layer was washed with three portions of 3 N NaOH and brine, dried over $MgSO_4$, and concentrated *in vacuo* to near dryness as the product is volatile. Column chromatography (20% ethyl acetate/hexane) provided 18.60 g of 3-methoxyphenethyl alcohol as an amber liquid. 3-Methoxyphenethyl alcohol is also available from Aldrich Chemical Co. at $289/25 g (3-methoxyphenylacetic acid $111/100 g).

**2-(2-Bromo-5-methoxyphenyl)-1-ethanol.** To 7.0 g (46.1 mmol) of 3-methoxyphenethyl alcohol in 100 mL of $CHCl_3$ at 0 °C was added 2.61 mL (50.7 mmol) of $Br_2$ in 25 mL of $CHCl_3$ over 25 min. After 1 h the reaction was quenched by the addition of 10% $Na_2S_2O_5$, and the organic layer was removed, dried over $K_2CO_3$, and concentrated *in vacuo* to provide 8.5 g (80%) of 2-(2-bromo-5-methoxyphenyl)-1-ethanol as a yellow liquid: $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (d, $J$ = 8.8 Hz, 1H), 6.82 (d, $J$ = 3.1 Hz, 1H), 6.65 (dd, $J$ = 3.1, 8.8 Hz, 1H), 3.87 (t, $J$ = 6.6 Hz, 2H), 2.96 (t, $J$ = 6.6 Hz, 3H).

**2-(2-Bromo-5-methoxyphenyl)-1-iodoethane.** To 11.6 g (44.1 mmol) of triphenylphosphine in 250 mL of $CH_2Cl_2$ under argon was added 3.00 g (44.1 mmol) of imidazole followed by 11.2 g (44.1 mmol) of $I_2$ over 10 min. Upon complete dissolution of the $I_2$, 8.5 g (36.8 mmol) of 2-(2-bromo-5-methoxyphenyl)-1-ethanol in 60 mL of $CH_2Cl_2$ was added over 5 min. After 1 h, the reaction mixture was concentrated in vacuo and applied to a silica gel column. Elution with 10% chloroform/hexane provided 11.4 g (91%) of 2-(2-bromo-5-methoxyphenyl)-1-iodoethane as a colorless liquid: $^1$H NMR ($CDCl_3$) $\delta$ 7.40 (d, $J$ = 8.7 Hz, 1H), 6.77 (d, $J$ = 2.9 Hz, 1H), 6.69 (dd, $J$ = 2.9, 8.7 Hz, 1H), 3.78 (s, 3H), 3.36–3.29 (m, 2H), 3.25–3.18 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.77, 140.54, 133.35, 116.22, 114.21, 114.03, 55.36, 40.59, 3.08; IR (film) 3065, 3002, 2957, 2834, 1240 cm$^{-1}$.

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