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Asymmetric Synthesis of Enantioenriched (+)-Elaeokanine A

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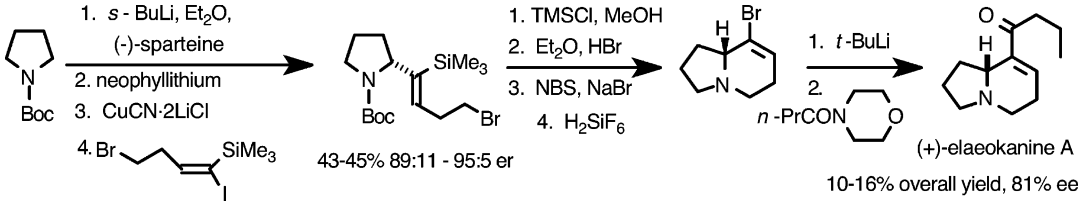

The key transformation in the total synthesis of (+)-elaeokanine A was accomplished by asymmetric deprotonation of *N*-Boc pyrrolidine, followed by the reaction of the in situ generated enantioenriched stereogenic cuprate reagent with (*E*)-4-bromo-1-iodo-1-trimethylsilyl-1-butene with retention of configuration. *N*-Boc deprotection, followed by a one-pot olefin isomerization and intramolecular amine alkylation afforded a bicyclic vinyl bromide that was converted into (+)-elaeokanine A by sequential halogen metal exchange and reaction of the organolithium reagent with *N*-butanoylmorpholine.

Introduction

The indolizidine alkaloids elaeokanine A (**1**), B (**2**), and C (**3**; Figure 1) were isolated from *Ekaeocarous kaniensis Schltr*., a large rain-forest tree found in New Guinea, along with the pyrrolo[2,1-f][1,6]naphthyridin-1(2*H*)-one tricyclic elaeokanidine alkaloids containing two nitrogen atoms.[1] Although elaeokanine A has been synthesized in racemic form numerous times,[2] only a few syntheses of the naturally occurring (+)-enantiomer have been reported.[3] Racemic synthetic routes to these compounds have largely involved iminium ion pathways,[2b,d,e,g−i,k] nitrone 1,3-dipolar additions,[2a,j,o] or imino Diels−Alder[2l,m] reactions, while the asymmetric routes have all employed chiral auxiliary methodology. Asymmetric routes to (+)-elaeokanine A have utilized chiral *N*-acylpyridinium salts (**4**),[3a] chiral sulfoxides (**5**),[3b] or a chiral maleimide derived from 10-mercaptoisoborneol,[3c] generating the natural product in 3−6% overall yields (Scheme 1). The chiral sulfoxide mediated route (i.e., **5**) actually provides for a more efficient synthesis of (−)-elaeokanine (i.e., 12% overall yield), because a $NaBH_4$ reduction of a bicyclic imine gives a 4:4:1:1 mixture of diastereomers, where 80% of the material can be converted to (−)-**1**.[3b]

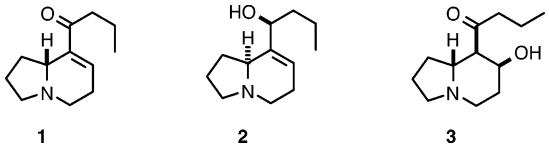

FIGURE 1. Naturally occurring (+)-elaeokanine A (1), (−)-B (2), and (−)-C (3).

Our development of α-(*N*-carbamoyl)alkylcuprate chemistry[4] provides for the rapid construction of *N*-heterocycles.[5] The method is particularly efficient for the synthesis of pyrrolizidine and indolizidine alkaloids,[6] where utilization of enantioenriched

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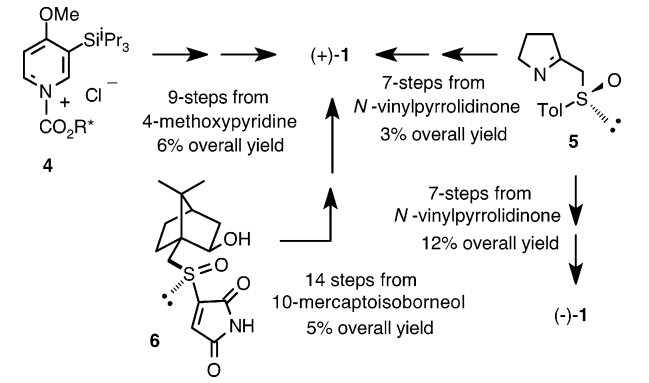
SCHEME 1



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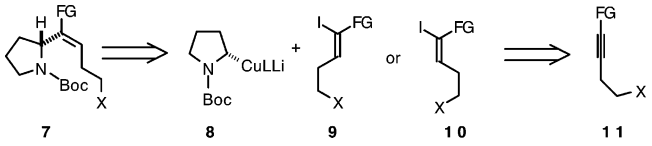

pyrrolidinylcuprates provides a protocol for asymmetric synthesis. We undertook a synthesis of (+)-elaeokanine A to explore the potential of *enantioenriched* stereogenic (i.e., a stereogenic carbon center bound to the copper atom) organocuprate reagents in target directed synthesis. Specifically, how would this methodology for the rapid introduction of the stereogenic center compare (i.e., in number of linear steps and final enantiopurity) with the chiral auxiliary based methods previously employed, and what types of problems might arise in the asymmetric reaction itself.

Results and Discussion

Focusing on α-(*N*-carbamoyl)alkylcuprate methodology, retrosynthetic analysis for **1** (Scheme 2) leads to the 2-(1-butenyl)-pyrrolidine derivative **7** containing a functional group (FG) for elaboration of the 1-oxobutyl side chain and a nucleofuge X for construction of the indolizidine skeleton via intramolecular cyclization. The substituted pyrrolidine **7** is potentially available from the enantioenriched stereogenic pyrrolidinyl cuprate **8** and the stereodefined vinyl iodide **9** or **10**, which in turn can be prepared from a bis-functionalized alkyne **11**. Elaeokanine A (**1**) contains the latent functionality necessary for conversion into elaeokanine B (**2**) and C (**3**), provided stereocontrol can be achieved. The ultimate length of this highly convergent route to the elaeokanines will hinge upon potential problems involving reactivity and stereocontrol.

The requisite vinyl mesylate **9** (FG = Me_3Si, X = OMs) was prepared from (*Z*)-4-iodo-4-trimethylsilyl-3-buten-1-ol[7] that was itself synthesized in three steps from commercially available 3-butyn-1-ol by established procedures.[8−10] The straightforward three-step preparation[8,9,11,12] of known (*E*)-vinyl iodide **10**[13] (FG = Me_3Si, X = Br) could be accomplished on a large scale (e.g., 100 mmol) and with excellent yields.

Vinylation of the bis-pyrrolidinylcuprate **8** (L = *N*-Boc-2-pyrrolidinyl) with (*Z*)-vinyl iodide **9** proved to be problematic as a result of the steric hindrance arising in the vinyl silane moiety, the reactive center being sterically encumbered both by the trimethylsilyl substituent and by the alkyl substituent cis to the iodide reactive center. All efforts to effect this transformation using either dialkylcuprates or alkylcyanocuprates **8** (L = CN) resulted in only trace amounts of the vinylation product (i.e., trans-diastereomer of **12**). Most of the starting *N*-Boc-pyrrolidine and some of the vinyl iodide were recovered.

Although the reaction of cuprate **8** (L = CN) with **10** (TMEDA, THF, −78 °C) gave low chemical yields, vinylation of the bis-pyrrolidinylcuprate **8** (L = *N*-Boc-2-pyrrolidinyl, TMEDA, THF) with **10** did afford **12** in 79% yield when the reaction mixture was allowed to warm slowly from −70 °C to room temperature. Loss of the starting vinyl iodide suggested that vinyl iodide decomposition pathways were competitive with the cuprate vinylation reaction. When the coupling reaction was carried out at −40 °C for several hours, the vinyl iodide decomposition pathways were suppressed and good yields of the coupling product could be obtained. These preliminary studies were performed in THF, which is not conducive to the formation of stable enantioenriched 2-lithio-*N*-Boc-pyrrolidine.[14] After optimization of the chemical yields was achieved, the asymmetric coupling reaction was examined.

Asymmetric deprotonation of *N*-Boc-pyrrolidine according to the Beak et al.[14] protocol [Et_2O, *s*-BuLi, (−)-sparteine, 1 h], followed by formation [i.e., CuCN·2LiCl, THF][15] of the enantioenriched stereogenic cuprate reagent **8** (L = *N*-Boc-2-pyrrolidinyl) and coupling with vinyl iodide **10** afforded coupled product **12** in various chemical yields and enantiomeric ratios (Table 1) depending upon reaction conditions. Utilization of the optimized procedure developed for the THF reactions in the Et_2O/THF solvent mixture (1:1) gave comparable chemical yields (Table 1, entry 1) but little to no enantioselectivity. Holding the reaction temperature at −78 °C for several hours resulted in lower chemical yields and similarly poor enantioselectivity (entry 2), although slightly better enantioselectivity could be achieved by holding the reaction mixture at −50 °C for 8 h (entry 3). Efforts to improve the enantioselectivity by employing pure Et_2O as solvent gave lower chemical yields and similar enantiomeric ratios (entry 4). In these experiments using Et_2O as solvent, the CuCN was solubilized with *n*-Bu_3P, because the use of a soluble source of Cu(I) salts is essential for cuprate formation at −78 °C. Utilization of higher reaction temperatures or slow cuprate formation results in racemization of the enantioenriched organolithium reagent.[15]

Aware that reductive elimination was suggested to be the slow step in cuprate mediated conjugate addition reactions,[16] we decided to explore the use of mixed cuprates containing a

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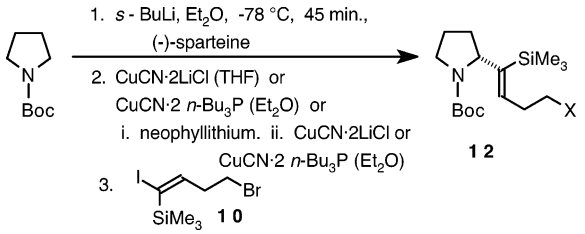
TABLE 1. Vinylation of *N*-Boc-pyrrolidinylcuprates with Vinyl Iodide 10



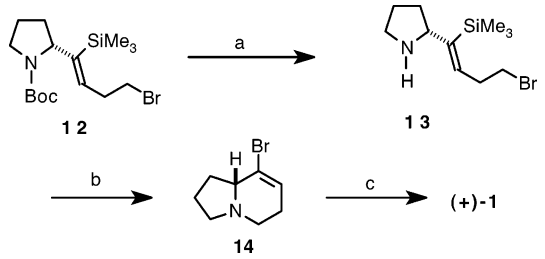
	reaction conditions				
entry	Cu(I) equiv[a]	solvent[b]	rxn temp °C (h)[c]	% yield[d] **12**	er[e]
1	0.5	A	−78 to 25 (12)	71−76	50:50−61:39
2	0.5	A	−78 (3)	47	50:50−55:45
3	0.5	A	−50 (8)	51	63:37
4	0.5	B	−78 (3)	41	67:33
5[f,g]	1.0	A	−78 to 25 (12)	58	60:40−63:37
6[f,h]	1.0	A	−78 to 25 (12)	67	75:25
7[f,h]	1.0	B	−78 to 25 (12)	43−45	89:11−95:5

[a] CuCN·2LiCl was employed and reactions were run on a 1.0 mmol scale unless otherwise noted. Cuprate formation was achieved at −78 °C for 1 h. [b] A = THF/Et_2O solvent ratio (1:1, v/v, unless otherwise noted), which arose by the deprotonation of carbamate in Et_2O, followed by the addition of a THF solution of CuCN·2LiCl. B = pure Et_2O arising by deprotonation of carbamate in Et_2O, followed by the addition of a Et_2O solution of *n*-Bu_3P·CuCN. [c] Temperature and time at which the cuprate/electrophile reaction was allowed to proceed. [d] Yields are based on products purified and isolated by flash column chromatography. [e] Enantioselectivity (e.g., er) was measured by chiral stationary phase HPLC on a Chiralcel OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [f] Neophyllithium was employed as a nontransferable ligand in dialkylcuprate formation. [g] Neophyllithium (2-phenyl-2-methylpropyllithium) was added to the solution of lithium (*S*)-*N*-Boc-2-pyrrolidinyl(cyano)cuprate. [h] Neophyllithium was added to the solution of (*S*)-*N*-Boc-2-pyrrolidinyllithium, followed by CuCN·2LiCl (THF) or *n*-Bu_3P·CuCN (Et_2O).

sterically hindered nontransferable ligand. Utilization of neophyllithium[17] (i.e., $PhCMe_2CH_2Li$) for generation of a mixed dialkylcuprate reagent (i.e., **8**; L = neophyl) resulted in formation of **12** with modest chemical yields and enantioselectivity with the THF/Et_2O protocol (Table 1, entry 5) when the neophyllithium reagent was added to **8** (L = CN). When CuCN·2LiCl was added to a mixture of (*S*)-*N*-Boc-2-pyrrolidinyllithium and neophyllithium, higher enantioselectivities were obtained (entry 6). When pure Et_2O was employed as solvent by dissolving CuCN in Et_2O with the aid of 2.0 equiv of *n*-Bu_3P and the resulting *n*-Bu_3P·CuCN was added to a mixture of (*S*)-*N*-Boc-2-pyrrolidinyllithium and neophyllithium, the enantiomeric ratio of **12** was increased up to 95:5 (entry 7). Although the chemical yield decreased with this mixed dialkylcuprate, this reagent efficiently required only one stereogenic pyrrolidinyl ligand, and the enantioselectivity of the reaction improved to synthetically useful levels.

Successful enantioselective construction of key intermediate **12** set the stage for indolizidine ring formation and introduction of the 1-oxobutyl side chain. The tactical necessity of employing vinyl iodide **10** with the incorrect olefin geometry required olefin isomerization for eventual annulation leading to the indolizidine ring system. Attempted isomerization of the double bond in **12**

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) MeOH, TMSCl, 12 h. (ii) $NaHCO_3$, CH_2Cl_2 extract (95%). (b) (i) Et_2O, HBr (1.1 equiv). (ii) NBS, NaBr. (iii) H_2SiF_6 (67%). (c) (i) *t*-BuLi, THF. (ii) *N*-butanoylmorpholine (53−80%).

from the (*Z*)-geometry to the (*E*)-geometry by irradiation with a UV sun lamp in the presence of *N*-bromosuccinimide (NBS) and pyridine proved unsuccessful, giving only recovered starting material.[18] The ready conversion of a mixture of (*E*)- and (*Z*)-γ-amino-α,β-enones to pyrroles[19] suggested the possibility of facile isomerization of α,β-enones under cyclization conditions. To this end, attempted acylation of vinyl silane[20] **12** with *n*-butanoyl chloride gave a 20:80 mixture of starting material and a new product in which the *N*-Boc protecting group was replaced with the *N*-butanoyl group.[21] This transformation suggested that *N*-Boc deprotection and *N*-acylation were significantly faster than acylation of the vinyl silane moiety.

At this point, we attempted to invert the olefin configuration and introduce a vinyl bromide functionality for subsequent synthetic elaboration by a bromination−desilylbromination sequence. Addition of bromine to **12**, followed by treatment of the reaction mixture with tetrabutylammonium fluoride, afforded a complex mixture of products,[22] as did a reported procedure[12] for the isomerization of vinyl silanes. Deprotection of *N*-Boc-pyrrolidine **12** with methanolic HCl (TMSCl/MeOH) gave, after neutralization, pyrrolidine **13** in nearly quantitative yield (Scheme 3). Conversion of **13** to the hydrobromide salt followed by addition of NBS and NaBr afforded, after quenching with fluosilicic acid, vinyl bromide **14** in 67% yield.

Vinyl bromide **14** was a key intermediate in the synthesis by Overman et al.[2e,i] of racemic elaeokanine A and involved the reaction of the vinyllithium reagent generated from **14** with butanal to give elaeokanine B (1:1 mixture of diastereomers), followed by oxidation of elaeokanine B to elaeokanine A. Enantioenriched **14** was readily converted to (+)-elaeokanine A by halogen−metal exchange and acylation with *N*-butanoylmorpholine (Scheme 3). The synthetic material gave ^1H NMR spectral data in agreement with the published data.[1,3a] Comparison of the optical rotation ($[\alpha]^{22}_D$ +38.2 (*c* 1.5, CH_2Cl_2)) with the reported literature value [synthetic, ($[\alpha]^{23}_D$ +47 (*c* 0.31 in $CHCl_3$),[3a] ($[\alpha]^{22}_D$ +49 (*c* 0.5 in $CHCl_3$)[3b,] ; isolated,[1] $[\alpha]_D$ +13 (*c* 0.9 in $CHCl_3$)] indicated an enantiomeric ratio of 89:11, which was identical to the enantiomeric ratio achieved in the vinylation of (*S*)-*N*-Boc-2-pyrrolidinylcuprates under the optimal conditions (Table 1, entry 7). Although the correlation of optical purity with enantiomeric ratio can be problematic,[23]

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(21) A (M + 2) parent molecular ion in the GC-MS trace [*m*/*z* 345 (5), 347 (5)] and a methyl absorption in the ^1H NMR spectrum [δ 2.75 (t, J = 7.2 Hz, 3H)] are consistent with the assigned structure.

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consistency between the chiral HPLC determination of the enantiomeric ratio for **12** and the optical purity measured for synthetic (+)-**1** appears to be reliable[24] given the unlikely isomerization of the stereogenic center in the transformations after its generation.

Conclusions

The convergent asymmetric synthesis of (+)-elaeokanine A in four linear steps from an enantioenriched stereogenic cuprate regent and (*E*)-4-bromo-1-iodo-1-trimethylsilyl-1-butene, itself prepared in three steps, has been achieved in 10−16% overall yield (using the lowest and highest yields for each transformation, respectively, obtained over several experiments) with an optical purity of 81% (90.5:9.5 er). The synthesis demonstrates the power of enantioenriched stereogenic *N*-Boc-2-pyrrolidinylcuprates for the rapid asymmetric synthesis of functionalized indolizidine alkaloids. The key copper-mediated asymmetric carbon−carbon bond-forming reaction occurs between two sterically hindered ligands, which proved problematic with regard to chemical yields and enantioselectivity. The utilization of a sterically hindered nontransferable ligand to significantly improve the enantioselectivity of the reaction may provide a general strategy for controlling enantioselectivity in enantioenriched stereogenic organocuprate reactions.

Experimental

(1,1-Dimethylethyl)-(*R*)-2-[(*Z*)-4-bromo-1-(trimethylsilyl)-1-butenyl]-1-pyrrolidinecarboxylate (12). *N*-Boc-pyrrolidine (0.855 g, 5.0 mmol) was dissolved in freshly distilled diethyl ether (15.0 mL) along with (−)-sparteine (1.345 g, 5.5 mmol). The reaction mixture was cooled to −78 °C under an argon atmosphere and *sec*-BuLi (2.5 mL, 2.2 M, 5.5 mmol) was added dropwise by syringe. The resultant solution was stirred at −78 °C for 1 h. Then the neophyllithium (5.0 mL, 5.0 mmol) was added at −78 °C, followed by the slow addition of a solution containing CuCN (450 mg, 5.0 mmol) and *n*-PBu_3 (2.02 g, 10.0 mmol) in diethyl ether (15.0 mL) via syringe. Stirring was continued at −78 °C for 30 min before the addition of vinyl iodide **10** (1.83 g, 5.5 mmol). The mixture was allowed to stir at −78 °C for 1 h. Then the reaction mixture was warmed to room temperature overnight. It was diluted with Et_2O (30 mL) and quenched with 5% aqueous HCl (15 mL). After shaking vigorously, the layers were separated. The aqueous layer was extracted with Et_2O (20 mL) three times, and the combined organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil that was purified by column chromatography [silica gel, R_f 0.35, petroleum ether/EtOAc, 80:20, v/v] as a clear, colorless oil (0.85 g, 45%): IR (neat) 2965 (br s), 2863 (w), 1683 (vs), 1401 (vs), 1265 (s), 1179 (s), 829 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.23−1.37 (br s, 9H), 1.75−2.02 (m, 4H), 2.69 (t, J = 7.2 Hz, 2H), 3.32 (t, J = 7.2 Hz, 2H), 3.34−3.39 (m, 2H), 4.35−4.47 (m, 1H), 5.68 (t, J = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.2, 21.3, 28.4, 32.1 (31.7, rotamer), 32.5, 34.6 (34.4, rotamer), 46.6 (46.9, rotamer), 61.0 (61.3, rotamer), 78.7, 134.0, 143.6, 154.2 (154.0, rotamer); mass spectrum *m*/*z* (relative intensity) EI 377 (1), 375 (1), 306 (73), 304 (73), 114 (100), 70 (85), 57 (65); High-resolution mass spectrum *m*/*z* calcd for $C_{16}H_{30}BrNO_2Si$, 375.1229; found, 375.1235 (M+).

The enantiomeric purity of **12** was determined by chiral stationary phase HPLC on a Chiracel OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 95:5 er [hexane/i-PrOH, 99:1 (v/v), flow rate at 0.5 mL/min, detection at λ = 210 nm]. The major enantiomer eluted first with a retention time of 11.7 min, followed by the minor isomer at 12.6 min.

(*R*)-2-[(*Z*)-4-Bromo-1-(trimethylsilyl)-1-butenyl]pyrrolidine (13). Carbamate **12** (375 mg, 1.0 mmol) was dissolved in methanol (5.0 mL) at 25 °C, and trimethylsilyl chloride (TMSCl, 540 mg, 5.0 mmol) was added dropwise by syringe. The mixture was stirred at room temperature overnight, then quenched with saturated aqueous $NaHCO_3$ until pH > 8. The mixture was diluted with methylene chloride, two layers were separated, and the organic layer was extracted three times with methylene chloride and dried ($MgSO_4$). Concentration in vacuo gave **13** as a clear, colorless liquid (0.268 g, 97%): IR (neat) 3427 (br s), 2957 (s), 2769 (w), 1632 (s), 1265 (s), 863 (s), 761 (s), 649 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.70−1.77 (m, 1H), 1.96−2.19 (m, 3H), 2.69−2.81 (m, 2H), 3.37−3.43 (m, 2H), 3.44−3.49 (m, 3H), 4.18 (br s, 1H), 6.35 (t, J = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.2, 22.8, 31.7, 32.8, 34.9, 45.1, 62.3, 137.5, 140.4; mass spectrum *m*/*z* (relative intensity) EI 262 (4), 260 (4), 196 (12), 70 (100).

(*R*)-8-Bromo-1,2,5,6,8a-hexahydroindolizine (14). To a solution of **13** (276 mg, 1.0 mmol) in diethyl ether (10 mL) at 0 °C was added aqueous HBr (0.15 mL, 1.1 mmol). The solution was stirred for 5 min, followed by the addition of NaBr (123 mg, 1.2 mmol) and NBS (214 mg, 1.2 mmol) in one portion at 0 °C and then warmed to room temperature over 30 min. Then, after a few minutes, H_2SiF_6 (0.5 mL, 1.1 mmol) was added dropwise. The reaction mixture was stirred for 12 h at room temperature, diluted with methylene chloride (10 mL), and washed with saturated $NaHCO_3$ (5 mL). After gentle shaking, the organic layer was separated, and the aqueous layer was exacted three times with methylene chloride (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Kugelrohr distillation (60 °C, 30 mmHg) of the residue gave **14** as a clear colorless liquid (136 mg, 67%): IR (neat) 2951 (w), 1634 (s), 1453, 1247, 843 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74−1.83 (m, 2H), 2.03−2.13 (m, 3H), 2.34−2.49 (m, 1H), 2.80−2.97 (m, 4H), 3.60−3.65 (m, 1H), 6.05 (t, J = 2.8, 1H); ^{13}C NMR ($CDCl_3$) δ 126.9, 126.4, 63.8, 50.7, 44.9, 30.3, 24.9, 22.7; mass spectrum *m*/*z* (relative intensity) EI 203 (29, $M^+ + 1$), 201 (30), 202 (30, M^+), 200 (30), 175 (32), 173 (32), 122 (100). [lit.[2i] ^{13}C NMR δ 126.9, 63.7, 50.7, 44.7, 30.3, 24.9, 22.7].

(+)-Elaeokanine A (1). To a dry 25 mL round-bottom flask equipped with a nitrogen inlet and kept under a static pressure of nitrogen was added **14** (100 mg, 0.5 mmol) and anhydrous THF (5 mL). The solution was cooled to −78 °C, followed by the slow addition of *t*-BuLi via syringe (0.55 mL, 1.8 M, 1.0 mmol) at −78 °C. Stirring was continued for 1 h at −78 °C. Then *N*-butanoylmorpholine was added (94 mg, 0.6 mmol) dropwise, followed by warming up to room temperature over 2 h. The reaction mixture was diluted with diethyl ether. Then 10 N HCl (0.20 mL) was added to give a cloudy suspension; the organic solvent was evaporated to yield a hydrochloride salt. The salt was treated with 10% K_2CO_3, and the mixture was extracted with methylene chloride twice. The combined CH_2Cl_2 extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **1** (58 mg, 60%; 60−80% in several experiments on racemic material) after flash column chromatography [Et_3N/MeOH/CH_2Cl_2, 1:1:98] purification: $[\alpha]^{22}_D$ = +38.2 (*c* 1.5, $CHCl_3$), [synthetic, $[\alpha]^{23}_D$ +47 (*c* 0.31 in $CHCl_3$),[3a] $[\alpha]^{22}_D$ +49 (*c* 0.5 in $CHCl_3$)[3b]; isolated,[1] $[\alpha]_D$ +13 (*c* 0.9 in $CHCl_3$)]; IR (neat) 3320 (br), 2995, 1668 (s), 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.31−1.42 (m, 1H), 1.61 (q, J = 7.2 Hz, 2H), 1.71−1.95 (m, 3H), 2.23−2.48 (m, 3H), 2.56 (dt, J = 8.8, 1.9 Hz, 2H), 2.70−3.00 (m, 3H), 3.56 (t, J = 1.8 Hz, 1H), 6.89 (t, J = 1.8 Hz, 1H); mass spectrum *m*/*z* (relative intensity) EI 193 (16, M^+), 178 (15), 164 (17), 150 (100), 122 (42); high-resolution mass spectrum *m*/*z* calcd for $C_{12}H_{19}NO$,

(23) Gawley, R. E. *J. Org. Chem.* **2006**, *71*, 2411−2416.

(24) The specific rotation can vary with concentration, temperature, solvent, and the presence of soluble impurities in the sample. The optical and enantiomeric purities may be nonequivalent (Horeau effect), although this is generally a small effect observed in weakly polar solvents that disappears in polar solvents. In a recent synthesis of pseudoheliotridane, the optical rotation of a mixture of diastereomers showed a small nonlinearity over a 4-fold range of concentrations, and the calculated optical purity showed an excellent agreement with the enantiomeric ratio measured for a key intermediate (see ref 6b).

193.1467; found, 193.1469 (M^+). ^{1}H NMR data are in agreement with published spectra.[3b,c]

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Supporting Information Available: General experimental information, materials, ^{1}H and ^{13}C NMR spectra for **10**, **12**−**14**, ^{1}H NMR spectrum for (+)-**1**, chiral HPLC trace for (*R*)-**12**, and GC-MS trace for (+)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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