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An improved synthesis of ethyl *cis*-5-iodo-*trans*-2-methylcyclohexanecarboxylate, a potent attractant for the Mediterranean fruit fly

Ashot Khrimian,[a,*] Armenak Kh. Margaryan[a] and Walter F. Schmidt[b]

[a]*USDA-ARS, Beltsville Agricultural Research Center, PSI, CAIBL, Bldg. 007, Rm. 301, Beltsville, MD 20705, USA*
[b]*USDA-ARS, Beltsville Agricultural Research Center, EQL, Beltsville, MD 20705, USA*

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Abstract—Both racemic ethyl 5-iodo-2-methylcyclohexanecarboxylate (**1**), known as Mediterranean fruit fly attractant ceralure B_1, and its (−)-(1*R*,2*R*,5*R*) enantiomer **1a** were conveniently synthesized from commercially available racemic *trans*-6-methyl-3-cyclohexenecarboxylic acid **2** or its (1*R*,6*R*) enantiomer **2a**. Key steps included an asymmetric Diels–Alder reaction using a sultam auxiliary and cyclization of the unwanted *trans*-5-iodo-*trans*-2-methylcyclohexanecarboxylic acid (**8**) to the intermediate lactone **7** (or **8a** to **7a**). The new method may circumvent chromatographic separations and seems amenable to scale-up. Published by Elsevier Science Ltd.

1. Introduction

The Mediterranean fruit fly, or medfly, *Ceratitis capitata* (Wiedemann), is a serious pest of over 253 varieties of fruits and vegetables. The establishment of this exotic pest in the continental United States would significantly increase pesticide use and curtail fruit and vegetable exports, a multibillion dollar industry.[1] For more than 30 years, conventional monitoring systems have utilized traps baited primarily with trimedlure, a synthetic male medfly attractant.[2] Trimedlure is a mixture of 16 regio- and stereoisomers of *tert*-butyl esters of 4(5)-chloro-2-methylcyclohexanecarboxylate, and over one million dispensers, each containing 2 g of trimedlure, are produced and sold annually for use as baits. An iodo analog of trimedlure, ceralure, also a mixture of 16 regio- and stereoisomers, has been found to be more persistent and more potent than trimedlure.[3] Field tests with individual ceralure isomers demonstrated that ethyl *cis*-5-iodo-*trans*-2-methylcyclohexanecarboxylate (ceralure B_1, **1**) is the most active component in the mixture,[4] and that ceralure B_1 is two to three times more attractive than trimedlure.[5]

A regioselective synthesis of racemic ceralure B_1 that produced a mixture of **1** with a *trans*-5-iodo isomer was described.[6] A chromatographic separation of two stereoisomers was reported,[6] but in our hands flash chromatography failed to isolate **1** quantitatively, and the use of HPLC deemed impractical for large scale synthesis. Raw and Jang have conducted syntheses of both enantiomers as well as of racemic ceralure B_1 (**1**) and found that (−)-(1*R*,2*R*,5*R*)-**1a** was a much better attractant than the (+) enantiomer and was 30–40% more active than the racemate **1**.[7,8]

The enantioselective synthesis, based on a chiral Diels–Alder reaction, utilized an expensive starting material, D-phenylalanine, and provided an overall yield of 15% from a nine step process.[7] We now report a new synthesis, amenable to both racemic (**1**) and (−)-ceralure B_1 (**1a**) production, that uses the relatively inexpensive (−)-bornane-10,2-sultam **3** as a chiral auxiliary for the Diels–Alder reaction. The new route provides better yields than existing methods, is easy to perform, and seems suitable for scale-up.

2. Results and discussion

As in the published syntheses,[6,7] our starting material was *trans*-6-methyl-3-cyclohexanecarboxylic acid (**2**, Siglure acid), the racemic form of which is commercially available. To prepare (−)-Siglure acid **2a**, we employed a Diels–Alder reaction using a chiral camphor-derived sultam auxiliary developed by Oppolzer, et al.[9] (Scheme 1). Usually, the acylation of amides, and particularly crotonylation of sultam **3**, requires a base such as sodium hydride.[9] Recently, we succeeded in conducting a direct acylation of sultam **3** with acryloyl chloride catalyzed by copper(II) chloride,[10] which rendered unnecessary the customary trimethylsilylation of the sultam prior to a copper-catalyzed

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* Corresponding author. Tel.: +1-301-504-6138; fax: +1-301-504-6580; e-mail: khrimiaa@ba.ars.usda.gov

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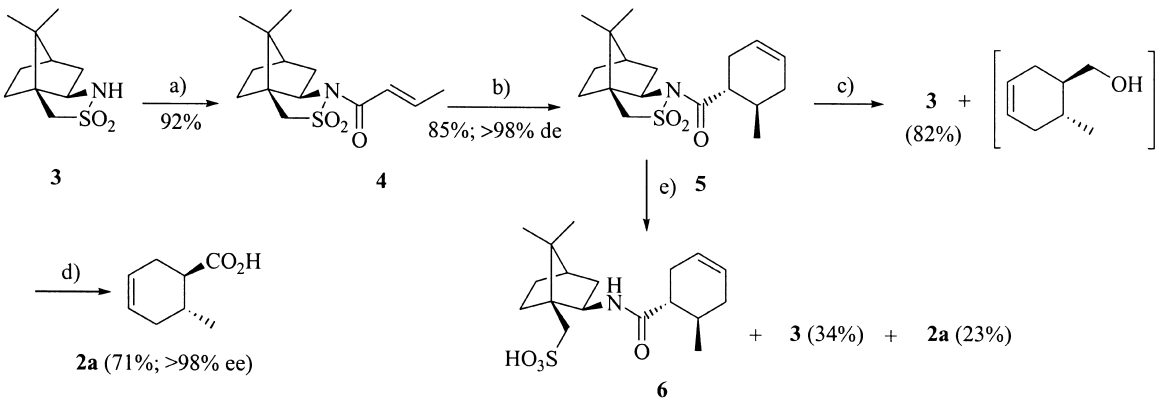
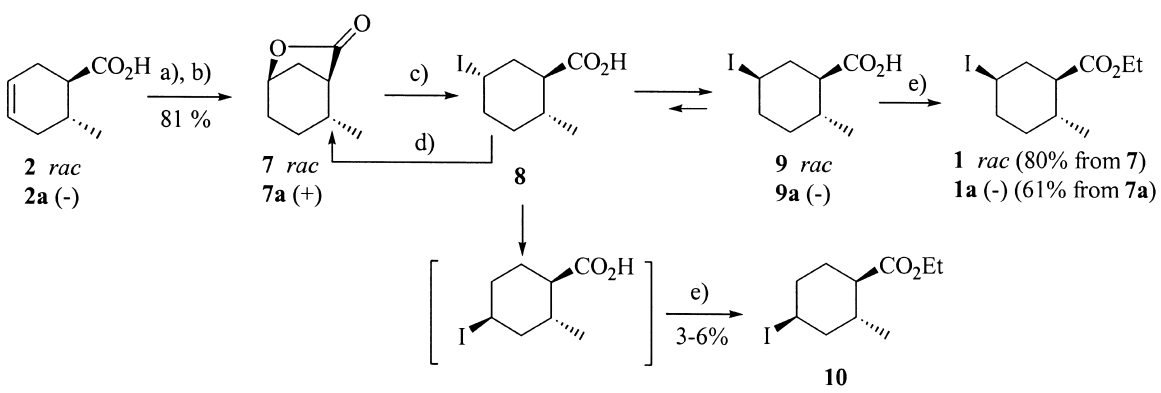


Scheme 1. *Reagents and conditions*: (a) *trans*-$CH_3CH{=}CHCOCl/Cu^{2+}$, reflux; (b) $CH_2{=}CHCH{=}CH_2$, $EtAlCl_2$, CH_2Cl_2, −50 to 0°C; (c) 1. LAH, THF, rt; (d) PDC, DMF, rt; (e) H_2O_2, LiOH, THF/H_2O, rt.

acylation.[11] We again were able to omit the silylation step, as (−)-bornane-10,2-sultam (**3**) was directly acylated with *trans*-crotonyl chloride in 92% yield in the presence of $CuCl_2$. A Lewis acid catalyzed Diels–Alder reaction of (−)-*N*-acylated sultam **4** and butadiene was performed using a protocol developed to suppress the polymerization of the diene by adding the radical inhibitor galvinoxyl.[12] Although in our hands some polymerization still occurred, the crystalline adduct **5** was isolated in 85% yield and >98% de judged from the absence of the signals of the other diastereoisomer in ^1H NMR spectrum. The stereochemistry of the newly constructed ring was assigned based on a well-documented sense of asymmetric induction expected from (−)-bornane-10,2-sultam auxiliary.[9,12]

We encountered certain difficulties during the cleavage of adduct **5** to (−)-Siglure acid **2a** (and recovering chiral auxiliary **3**). An obvious solution would have been base-catalyzed hydrolysis reported for the Diels–Alder adduct of *N*-propenoyl-2,10-camphorsultam and butadiene.[9,12] However, hydrolysis of **5** with lithium hydroxide in aqueous THF[9] was unsuccessful, as were attempts to use other bases or to promote the reaction by ultrasound and/or phase-transfer catalysis. Apparently, a methyl group in the newly constructed ring exerts significant steric crowding in the vicinity of carbonyl function, similar to the steric shielding of the exocyclic carbonyl group in certain Diels–Alder adducts with an oxazolidinone chiral auxiliary.[13,14] In the latter case, lithium hydroperoxide was reportedly the reagent of choice for regioselective hydrolysis of sterically hindered carboximides.[13,14] We found that unlike lithium hydroxide, lithium hydroperoxide did hydrolyze adduct **5**, but the yields of both **2a** and sultam **3** were low. The main product was a water-soluble material identified on the basis of ^1H NMR and IR spectra as sulfonic acid **6**, arising from a somewhat unexpected cleavage of the S–N bond. The main evidence from ^1H NMR in favor of structure **6** was a substantial difference in chemical shifts of the magnetically non-equivalent protons in $CH_AH_BSO_2$ (δ 2.92 and 3.31), similar to that of (+)-10-camphorsulfonic acid (δ 2.82 and 3.33). Furthermore, the IR spectrum showed absorptions characteristic for structure **6** (See Section 3). For the conversion of **5** to **2a**, we used a slightly modified version of a two-step procedure reported by Oppolzer et al.[9] Adduct **5** was first reduced with LAH in THF to give sultam **3** and intermediate 6-methyl-3-cyclohexenemethanol, and the later was oxidized in situ with pyridinium dichromate in DMF[15] to give **2a**. Extractive separation of the products followed by chromatography afforded 71% (−)-Siglure acid **2a** of >98% ee and 82% of **3**. Thus, the chiral auxiliary could be efficiently recovered for further use.

The synthesis outlined in Scheme 2 was first developed using racemic Siglure acid **2**. The method was based on the route of Avery et al.[6] and was further improved by recycling the unwanted stereoisomer. Sequential iodolactonization of acid **2** and reduction of iodolactone according to published methodology[6,7] yielded lactone **7**. For ring opening of **7**, we



Scheme 2. *Reagents and conditions*: (a) KI_3, $NaHCO_3$; (b) $(Bu)_3Sn$, AIBN, benzene, reflux; (c) 1. Cl_3SiCH_3/NaI, CH_3CN, reflux, 2. H_2O; (d) K_2CO_3, THF; (e) 1. $(COCl)_2$, DMF, CH_2Cl_2. 2. EtOH, Py.

used methyltrichlorosilane/sodium iodide mixture,[16] which appeared to be more efficient than chlorotrimethylsilane/sodium iodide.[6] Initially, acid **8** formed almost exclusively (after hydrolysis of the intermediate silyl ester). Apparently, cleavage of lactone **7** occurrs stereoselectively with inversion of configuration at C-3. As the reaction advances, acid **8** slowly isomerizes to acid **9**, and continuing the reaction for 3–4 h results in the two epimers in the ratio of 2:3. Longer runs gave rise to byproducts and did not seem to change the proportion of stereoisomers. We found that heating pure acid **9** in the presence of Cl_3SiCH_3 (1 equiv.) and NaI (3 equiv.) in CH_3CN, or just in a solution of NaI (2 equiv.) in CH_3CN, for 7–8 h resulted in mixtures of **9** and **8** containing 30–40% of the latter.† Similarly, ceralure B_1 **1** upon reflux with NaI (2 equiv.) in CH_3CN for 12 h gave a mixture of **1** and the *trans*-3-iodo epimer in the ratio of 2:1.† We also found that heat itself did not cause epimerization, as acid **9** melted at 165°C without change, and epimer **8** upon melting at 89°C partially cyclized to lactone **7** but did not form acid **9**. We therefore concluded that interconversion of epimers **8** and **9** (as silyl esters) during cleavage of **7** is catalyzed by iodide, apparently through an S_N2 type displacement of the existing iodine atom at C-3. The 5-*cis*-iodo isomer **9** appears to be thermodynamically more stable than the 5-*trans* epimer **8**. A minor side reaction (Scheme 2) concurrently afforded 3–6% of 4-iodo regioisomer **10**, evidently through an HI elimination–addition sequence.

It was mentioned earlier that the stereoisomer **1** was the most attractive to the medfly among all regio- and stereoisomers of the ceralure mixture, which necessitated finding an efficient way of purifying acid **9**. We found that a short reflux of the acid mixture with potassium carbonate in THF resulted in complete cyclization of epimer **8** to lactone **7**, whereas **9** remained intact. Separation of acid **9** and lactone **7** was easily achieved by partitioning between aqueous K_2CO_3 (pH ~8–9) and ether/hexane (1:1). Consequently, successive ring opening of lactone **7** and reconverting the unwanted acid **8** to starting material achieved a conversion of ~60% and provided acid **9** of 92–94% purity. In the last step, acid **9** was esterified to Ceralure B1 which was isolated by flash chromatography in 80% yield based on reacted lactone **7**. Alternatively, pure acid **9** could be obtained by crystallization and subsequently converted to ester **1** in 72% yield, thus excluding chromatography throughout the synthesis. Notably, both chromatography and crystallization conveniently removed regioisomer **10** from the main product. The overall yield of racemic ceralure B_1 **1** starting from Siglure acid was 58–65%, compared to 30–35% yield achieved in previous syntheses.

Analogously to the achiral synthesis, (−)-**2a** was converted to (+)-(1*R*,2*R*,5*R*)-**7a** in 75% yield.[7] Treatment of **7a** with Cl_3SiCH_3/NaI for 2 h followed by recycling of iodoacid **8a** using the described protocol afforded (−)-(1*R*,2*R*,5*R*)-iodoacid **9a** in 64% yield after crystallization from heptane. Finally, **9a** was esterified to (−)-ceralure B_1 **1a** in an overall yield of 46% based on **2a**, and 26% based on (−)-bornane-10,2-sultam **3**.

In summary, a convenient and easily scaleable synthesis of both racemic and (−)-ceralure B_1 was developed. Inasmuch as racemic ceralure B_1**1** is only 30–40% less attractive than the (−)-enantiomer **1a**, the former appears commercially appealing. It is now being scaled-up to kilogram quantities for larger field studies.

3. Experimental

3.1. General

Melting points and boiling points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as an internal standard on a Bruker QE-300 spectrometer. GC analyses were performed on a Shimadzu 17A gas chromatograph using a 60 m×0.25 mm RTX-1701 column (Restek Corporation) and H_2 as a carrier gas. Optical purity of (−)-**2** was determined on Chiraldex B-DM GC column (β-cyclodextrin, dimethyl), 30 m×0.25 mm (Advanced Separation Technologies, Inc). Mass spectra were obtained with a Hewlett–Packard 5971 GC–MS equipped with a 30 m×0.25 mm DB-5 (J&W Scientific) column. Combustion analyses were conducted by Galbraith Laboratories. Flash chromatography was carried out with 230–400 mesh silica gel (Whatman). The reagents were bought from Aldrich unless otherwise specified. (−)-Bornane-10,2-sultam **3** was synthesized from (+)-camphorsulfonic acid by converting it to acyl chloride,[17] a two-step transformation to (−)-(camphorsulfonyl)imine,[18] and reduction with LAH.[19] Mention of a proprietary company or product does not imply endorsement by the US Department of Agriculture.

3.1.1. (−)-*N*-[(*E*)-2′-Butenoyl]bornane-10,2-sultam (4).[9] A solution of (−)-bornane-10,2-sultam **3** (26.4 g, 0.123 mol), *trans*-crotonyl chloride (47.3 mL, 0.491 mol) and anhydrous $CuCl_2$ (1.64 g, 0.012 mol) in anhydrous benzene (180 mL) was refluxed under N_2 for 1 h. The mixture was filtered while still warm, the reaction vessel was washed with dichloromethane (80 mL), and the combined filtrates were concentrated in vacuo to give a solid product. Crystallization from methanol (250 mL) yielded pure sultam (31.0 g, 89%) as white needles, mp 183–185°C. $[\alpha]_D$=−98.9 (*c* 1.60, $CHCl_3$). Lit.[9] mp 186–187°C, $[\alpha]_D$=−99.5 (*c* 1.04, $CHCl_3$). IR (KBr, cm $^{-1}$): 2910, 1680, 1640, 1450, 1380, 1330, 1225, 1135, 975, 880, 780, 760. ^{1}H NMR ($CDCl_3$): 0.95 (s, 3H), 1.14 (s, 3H), 1.25–1.47 (m, 2H), 1.85–2.20 (m, 5H), 1.90 (dd, *J*=7.0, 1.5 Hz, 3H), 3.42 (d, *J*=14.0 Hz, 1H), 3.48 (1H, d, *J*=14.0 Hz), 3.90 (dd, *J*=5.5, 7.0 Hz, 1H), 6.55 (dq, *J*=1.5, 15.0 Hz, 1H), 7.06 (dq, *J*=7.0, 15.0 Hz, 1H).

3.1.2. (−)-*N*-[(1′*R*,6′*R*)-6-Methyl-3-cyclohexenylcarbonyl]bornane-10,2-sultam (5). To a dry 250 mL flask equipped with a pressure-equalized dropping funnel, was cannulated a solution of **4** (5.66 g, 20.0 mmol) in anhydrous CH_2Cl_2 (43 mL) containing galvinoxyl (0.25 g). The resulting red-brown solution was cooled to −78°C, and $EtAlCl_2$ (3.2 mL, 30.4 mmol) in anhydrous CH_2Cl_2 (10 mL)

† 50–60 μmol scale reactions were run and worked-up as described in Section 3 and analyzed by GC.

was added slowly via the dropping funnel keeping the temperature at −78°C. The bright pink mixture was then stirred at −78°C for 15–20 min after which time gaseous butadiene (275.2 mmol corresponding to 24 mL of liquid) was added via a cannula whose tip was submerged into the reaction mixture. After addition was complete the mixture was allowed to warm up to 0°C and kept at this temperature overnight. The resulting pink solution was transferred into stirred ice-water (100 mL) to give a bright yellow mixture from which the organic phase was separated and washed with sat. brine (50 mL), sat. aq. $NaHCO_3$ (50 mL) and more brine (50 mL). The solution was dried ($MgSO_4$), filtered and concentrated to give a gummy yellow solid (8.07 g), which was dissolved in boiling heptane (125 mL). On cooling, Diels–Alder adduct **5** (4.90 g) crystallized as fine white plates. The mother liquor was concentrated and the residual gum chromatographed on silica gel (EtOAc/pet. ether, 1:8) to give an additional 0.90 g **5** (total 5.80 g, 86%), mp 181–183°C, $[\alpha]_D$=−159.3 (*c* 1.6, $CHCl_3$). IR (KBr, cm^{-1}): 3020 m, 2960 s, 2890 m, 2840 w, 1685 s, 1655 s, 1460 w, 1415 w, 1325 s, 1275 s, 1245 s, 1220 s, 1140 m, 1065 m, 1005 w. ^1H NMR ($CDCl_3$): 0.95 (s, 3H), 0.96 (d, *J*=6.0 Hz, 3H), 1.12 (s, 3H), 1.18–1.45 (m, 2H), 1.52–2.25 (m, 9H), 2.27–2.50 (m, 1H), 2.91 (ddd, J_1=5.5 Hz, J_2=J_3=10.5 Hz, CHC═O), 3.41 (d, *J*=14.0 Hz, $CH_AH_BSO_2$), 3.49 (d, *J*=14.0 Hz, $CH_AH_BSO_2$), 3.91 (dd, J_1=J_2=6.0 Hz, CHN), 5.55–5.93 (m, CH=CHHzCH). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.00; H, 8.00; N, 4.14. Found: C, 63.99; H, 7.97; N, 4.00.

3.1.3. (−)-(1*R*,6*R*)-6-Methyl-3-cyclohexenecarboxylic acid (2a). To a stirred suspension of lithium aluminum hydride (152 mg, 4.0 mmol) in anhydrous THF (10 mL) was added dropwise a solution of **5** (1.38 g, 4.0 mmol) in anhydrous THF (10 mL) under N_2 over a period of 20 min. The reaction mixture was stirred at room temperature for 4 h, then unreacted lithium aluminum hydride was cautiously hydrolyzed by dropwise addition of 1N hydrochloric acid (30 mL). Layers were separated and the aqueous phase was extracted with methylene chloride (5×25 mL). The organic washings were combined with the THF layer, dried with $MgSO_4$ for 1 h and concentrated to give a crude product (1.38 g) that was dissolved in DMF (28 mL) and stirred with pyridinium dichromate (7.62 g, 20.2 mmol) for 4 h at room temperature. The reaction mixture was diluted with water (70 mL) and extracted with diethyl ether (5×100 mL). The combined extract was concentrated to ~200 mL and washed with 10% aqueous sodium carbonate (2×25 mL). The aqueous layer was cooled in an ice-water bath, acidified with conc. HCl to pH 1–2 and extracted with methylene chloride (5× 50 mL). The extract was dried with $MgSO_4$, concentrated on a rotary evaporator and flash chromatographed (EtOAc/hexane, 1:3) to give acid (−)-**2** (0.412 g, 72%) of >98 % ee determined by analysis of methyl ester (CH_2N_2) on a chiral GC column. The ether layer was dried ($MgSO_4$), concentrated, and flash chromatographed (acetone/hexane, 1:4) to recover pure sultam **4** (0.716 g, 82%).

3.1.4. Hydrolysis of Diels–Alder adduct 5 with lithium hydroperoxide. To a cold (0°C) solution of **5** (1.69 g, 5.0 mmol), in 3:1 THF/water mixture (16 mL) was added 30% hydrogen peroxide (2.85 mL, 25 mmol), followed by solid lithium hydroxide monohydrate (0.42 g, 10 mmol). The resulting solution was allowed to warm to room temperature and was stirred for 17 h. The reaction mixture was cooled to 0°C, and a solution of sodium sulfite (3.53 g, 27.9 mmol) in water (15 mL) was added. After buffering to pH 9–10 by addition of saturated aqueous $NaHCO_3$ (2 mL), the bulk of THF was removed in vacuo, and the resulting mixture was extracted with methylene chloride (3×25 mL). The combined methylene chloride extracts were dried ($MgSO_4$) and concentrated to yield a crude sultam **3** (0.37 g, 34%). The aqueous layer was acidified to pH 1–2 with 20% H_2SO_4 and extracted with ethyl acetate (4×25 mL). The combined ethyl acetate extract was dried ($MgSO_4$), concentrated and purified by flash chromatography (EtOAc/methanol, 10:1) to give pure acid (−)-**2** (0.16 g, 23%) and *(+)-(1S,2R)-2-[(1′R,6′R)-6-methyl-3-cyclohexene-1′-carbonyl]aminobornane-10-sulfonic acid* (**6**, 0.23 g, 13%), mp 229°C (dec). $[\alpha]_D$=+ 89.7 (*c* 1.37, CH_3OH). IR (KBr, cm^{-1}): 3440 w, 3260 s and 3110 s (N–H), 2900 s, 1660 w, 1600 s, 1280 s and 1250 m (S═O asym.), 1080 m and 1050 s (S═O sym.), 975 m, 810 w, 680 m. ^1H NMR (CD_3OD): 0.95 (s, 3H), 1.01 (s, 3H), 1.02 (d, *J*=5.0 Hz, CH_3CH), 1.13–1.30 (m, 1H), 1.60–2.35 (m, 11H), 2.44 (ddd, J_1=5.5 Hz, J_2=J_3=10.5 Hz, CHC═O), 2.92 (d, *J*=15.0 Hz, $CH_AH_BSO_2$), 3.31 (d, *J*=15.0 Hz, $CH_AH_BSO_2$), 4.05 (dd, *J*=4.0, 8.5 Hz, CHN), 5.55–5.77 (m, CH═CH). Anal. Calcd for $C_{18}H_{29}NO_4S$: C, 60.76; H, 8.15; N, 3.93. Found: C, 60.65; H, 8.47; N, 3.91.

3.1.5. *trans*-2-Methyl-6-oxabicyclo[3.2.1]octan-7-one (7). Was prepared from *trans*-6-methyl-3-cyclohexene-1-carboxylic acid (Siglure acid, Pharma Tech International Corp.) via the iodolactonization–reduction sequence described in the literature.[6,7] Iodolactone of 98% purity was obtained in 87% yield. MS (EI): 266 (M^+), 139, 95 (100), 79, 77, 67 matched literature data.[7] Crude iodolactone (54.35 g, 0.20 mol) was reduced with tributyltin hydride (68 mL, 0.25 mol) in benzene solution (250 mL) in the presence of 2,2′-azobisisobutyronitrile (70 mg) as described[7] to give crude lactone **7** (42.56 g). A sample (1.01 g) of the product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to give **7** (0.630 g) in 93% yield. The remainder was purified by distillation, bp 86–88°C/0.6 torr, to give **7** (18.91 g) of > 98% purity. MS (EI): 140 (M^+), 112, 97, 81 (100), 55, 41. Mp 58°C (hexane).

3.1.6. *cis*-5-Iodo-*trans*-2-methylcyclohexanecarboxylic acid (9). To a solution of **7** (3.50 g, 25 mmol) and sodium iodide (11.25 g, 75 mmol) in dry acetonitrile (80 mL), methyltrichlorosilane (2.95 mL, 25 mmol) was added under a N_2 atmosphere. The mixture was refluxed for 2 h, concentrated on rotary evaporator to remove most of the acetonitrile, and partitioned between water (100 mL) and ether (100 mL). The white precipitate was removed by vacuum filtration and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were washed with a small amount of 10% sodium thiosulfate solution to remove the color, filtered under vacuum, and dried with Na_2SO_4. Evaporation of the solvent left 6.4 g of the acids **9** and **8** in the ratio 53:43, as determined by treating an aliquot with diazomethane and GC analysis of the corresponding methyl esters. The mixture of acids was

dissolved in THF (100 mL), treated with anhydrous potassium carbonate (1.73 g, 12.5 mmol), and refluxed under N_2 for ~1 h, or until GC analysis showed complete conversion of acid **8** to starting lactone **7**. Most of the THF was removed under reduced pressure, water (50 mL) was added to the remainder, and the mixture was cooled to 0°C. A solution of K_2CO_3 (15 mL, 10%) was added under vigorous stirring bringing the pH to 8–9. The mixture was extracted while cold with hexane/ether, 1:1 (4×30 mL), the organic extract was neutralized with 2% H_2SO_4, dried with Na_2SO_4 and evaporated to recover starting **7** (1.40 g, 10 mmol, 97% purity). Thus, the conversion after consecutive ring opening and lactonization steps was 60%. The aqueous layer was acidified with 10% H_2SO_4 to pH 2, extracted with CH_2Cl_2 and dried with Na_2SO_4. Evaporation of CH_2Cl_2 afforded crude acid **9** (3.78 g, 92% purity) as a colorless solid, which was purified by crystallization from heptane (136 mL) to afford >98% pure acid **9** (3.14 g, 78% yield based on reacted lactone **7**). Mp 165°C. ^{1}H NMR (300 MHz, $CDCl_3$): 0.91 (d, J=6.5 Hz, CH_3), 1.13 (dddd, $^3J_{3a-2a}\approx{}^3J_{3a-4a}\approx{}^2J_{3a-3e}\approx$12.5 Hz, $^3J_{3a-4e}$=3.5, H-3a), 1.64 (dm, H-3e), 1.75 (m, H-2a), 1.90–2.10 (m, 2H, H-1, H-4a), 2.16 (ddd, $^3J_{6a-1a}\approx{}^3J_{6a-5a}\approx{}^2J_{6a-6e}$=12.5 Hz, H-6a), 2.42 (dm, $^2J_{4a-4e}$=12.0, H-4e), 2.61 (dm, H-6e), 4.03 (dddd, $^3J_{5a-4a}$=12.5 Hz, $^3J_{5a-6e}\approx{}^3J_{5a-4e}\approx$4.0 Hz, H-5a). ^{13}C NMR (76 MHz, $CDCl_3$): 20.1 (CH_3), 24.9 (C-5), 32.9 (C-2), 36.1 (C-3), 39.9 (C-4), 42.5 (C-6), 53.0 (C-1), 179.4 (COOH). NMR spectra are in close agreement with literature data of the corresponding ethyl ester.[20] Anal. Calcd for $C_8H_{13}IO_2$: C, 35.80; H, 4.90. Found: C, 36.09; H, 5.14.

3.1.7. Ethyl *cis*-5-iodo-*trans*-2-methylcyclohexanecarboxylate (1). To a solution of crude acid **9** (2.97 g, 92% purity, 11 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (1.93 mL, 22 mmol) at 0°C followed by dimethylformamide (10 μL). The mixture was stirred at room temperature for 2 h and concentrated on rotary evaporator. The remainder was taken into CH_2Cl_2 (18 mL), cooled to −10°C and treated with a mixture of ethanol (734 μL, 13 mmol) and pyridine (1.06 mL, 13 mmol). After stirring for 2 h at rt, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with water, 5% HCl, water and dried with Na_2SO_4. Evaporation of the solvent left Ceralure B1 (3.15 g) of 92% purity. A sample of crude product (1.05 g) was flash chromatographed (hexane/ethyl acetate, 19:1) to afford 930 mg **1** (R_f=0.4, 98% pure). The isolated yield of Ceralure B1 based on a two-step process from **7** and 60% conversion was 80%. GC retention times and mass-spectroscopy data of synthesized product and an authentic sample were identical. MS (EI) m/z: 251 (2%), 169 (15), 123 (10), 95 (100), 81 (12), 67 (22), 55 (25). Continuing elution with the same solvent furnished 30 mg ethyl *cis*-4-iodo-*trans*-2-methylcyclohexanecarboxylate (**10**, R_f=0.3). ^{1}H NMR (300 MHz, C_6D_6): 0.61 (m, H-3a), 0.69 (d, J=6.5 Hz, CH_3), 0.80 (m, H-5a), 0.86 (t, J=6.0 Hz, CH_2CH_3), 2.06 (dm, H-6e), 1.58–1.76 (m, 3H), 2.05 (dddd, $^3J_{6a-1a}\approx{}^3J_{6a-5a}\approx{}^2J_{6a-6e}$=11.5 Hz, $^3J_{6a-5e}$=3.5 Hz, H-6a), 2.32 (m, H-2a), 3.87 (q, CH_2CH_3), 4.16 (m, H-4e). ^{13}C NMR (76 MHz, $CDCl_3$): 14.3 (CH_3CH_2), 19.4 (CH_3), 26.0 (C-6), 30.4 (C-2), 32.8 (C-4), 35.5 (C-5), 43.7 (C-3), 50.7 (C-1), 60.2 (CH_3CH_2), 174.8 (C=O). ^{13}C NMR data were identical to those reported in the literature.[20]

3.1.8. *trans*-5-Iodo-*trans*-2-methylcyclohexanecarboxylic acid (8). To a solution of lactone **7** (1.00 g, 7.1 mmol) and NaI (3.15 g, 21 mmol) in acetonitrile (20 mL) was added under N_2 chlorotrimethylsilane (2.7 mL, 21 mmol). The mixture was refluxed for 30 min and quenched with ice-water. The reaction products were extracted with ether (3×20 mL), and the combined ether extracts were washed with sodium thiosulfate and dried with Na_2SO_4. Evaporation of the solvent provided a mixture of 32% starting lactone **7**, 5% acid **9** and 60% acid **8**. The mixture was suspended in water and treated with 10% K_2CO_3 at 0°C to pH ~9 and extracted with a 1:1 mixture of hexane and ether (4×20 mL) to separate unreacted lactone from acids. The aqueous layer was acidified with 10% H_2SO_4 to pH ~2 and extracted with CH_2Cl_2 (4×20 mL). After drying the extract with Na_2SO_4, the residue was purified by flash chromatography (hexane/ethyl acetate, 4:1, 0.01% trifluoroacetic acid) to afford 430 mg acid **8** of 97% purity, mp 86°C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.01 (d, J=6.5 Hz, CH_3), 1.47–1.85 (m, 5H, H-2a, 3a, 3e, 4a, 6a), 2.06 (m, 1H, H-4e), 2.25 (dm, $^2J_{6e-6a}$=14.5, H-6e), 2.55 (ddd, $^3J_{1a-6e}$=3.0 Hz, $^3J_{1a-2a}\approx{}^3J_{1a-6a}$=11.0 Hz, H-1a), 4.84 (m, 1H, H-5e), 11.15 (1H, OH). ^{13}C NMR (76 MHz, $CDCl_3$): 20.1 (CH_3), 30.2, 32.0, 33.7 (C-5), 35.6 (C-4), 38.8 (C-6), 47.4 (C-1), 181.5 (COOH). NMR spectra are in close agreement with literature data of the corresponding ethyl ester.[20] Anal. Calcd for $C_8H_{13}IO_2$: C, 35.80; H, 4.90. Found: C, 35.26; H, 4.99. Running the same reaction for 7–8 h resulted in complete conversion of **7** to a 42:53 mixture of **8** and **9**.

3.1.9. (+)-(1*R*,2*R*,5*R*)-2-Methyl-6-oxabicyclo[3.2.1]-octan-7-one (7a). Was prepared in overall 75% yield from (−)-**2a** acid via iodolactonization–reduction procedure described above for the racemic compound. Mp 58°C (hexane). $[\alpha]_D$=+33.3 (c 0.94, $CHCl_3$). Lit.[7] $[\alpha]_D$=+31.3 (c 0.96, $CHCl_3$).

3.1.10. (−)-(1*R*,2*R*,5*R*)-5-Iodo-2-methylcyclohexanecarboxylic acid (9a). To a solution of (+)-**7a** (3.59 g, 25.64 mmol), and NaI (11.54 g, 76.92 mmol) in dry acetonitrile (80 mL) was added methyltrichlorosilane (3.03 mL, 25.64 mmol) and the mixture was refluxed for 2 h. After the work-up described for the racemic compound, the crude mixture of acids **8a** and **9a** (7.67 g) was dissolved in THF (90 mL) and refluxed in the presence of K_2CO_3 for 50 min. Acid–base partitioning was conducted at 0°C as described above. Flash chromatography (hexane/ethyl acetate, 7:3) of crude basic material (2.68 g), yielded **7a** (1.27 g, 9.04 mmol). Crystallization of the acidic product (3.49 g) from heptane (120 mL) furnished pure **9a** (2.68 g, 10.67 mmol) in 64% yield based on reacted **7a**. $[\alpha]_D$=−55.6 (c 0.70, CH_2Cl_2), mp 175–177°C.

3.1.11. Ethyl (−)-(1*R*,2*R*,5*R*)-5-iodo-2-methylcyclohexanecarboxylate (1a). Analogously to the achiral synthesis, **9a** (2.23 g, 8.32 mmol) in CH_2Cl_2 (23 mL) was converted to acyl chloride using oxalyl chloride (16.21 mmol) and DMF (10 μL). The crude acyl chloride was esterified with EtOH (550 μL) in CH_2Cl_2 (14 mL) in the presence of pyridine (795 μL) to **1a** (2.34 g, 95% yield), $[\alpha]_D$=−33.1 (c 0.80, CH_2Cl_2). Lit.[7] $[\alpha]_D$=−29.0 (c 0.72, CH_2Cl_2).

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