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

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Abstract—Both racemic ethyl 5-iodo-2-methylocyclohexanecarboxylate (1), known as Mediterranean fruit fly attractant ceralure B1, and its (-)-(1R,2R,5R) enantiomer 1a were conveniently synthesized from commercially available racemic trans-6-methyl-3-cyclohexene-carboxylic acid 2 or its (1R,6R) enantiomer 2a. Key steps included an asymmetric Diels–Alder reaction using a sultam auxiliary and cyclization of the unwanted trans-5-iodo-trans-2-methylocyclohexanecarboxylic 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-methylcyclohexane-carboxylate, and over one million dispensers, each containing 2 g of trimedlure, are produced and sold annually for use as baits. An isodo 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-methylocyclohexanecarboxylate (ceralure B1, 1) is the most active component in the mixture,4 and that ceralure B1 is two to three times more attractive than trimedlure.5

A regioselective synthesis of racemic ceralure B1 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 B1 (1) and found that (−)-(1R,2R,5R)-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 B1 (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,5,7 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 the unwanted trans-5-iodo-trans-2-methylocyclohexanecarboxylic 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.

Keywords: medfly; ceralure; attractant; synthesis; racemic; asymmetric.

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acylation. We again were able to omit the silylation step, as \((\text{trans})\)-bornane-10,2-sultam \((3)\) was directly acylated with \((\text{trans})\)-crotonyl chloride in 92% yield in the presence of CuCl₂. A Lewis acid catalyzed Diels–Alder reaction of \((\text{N-acylated sultam} \ 4)\) and butadiene was performed using a protocol developed to suppress the polymerization of the diene by adding the radical inhibitor galvinoxyl. 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 \(^1\)H NMR spectrum. The stereochemistry of the newly constructed ring was assigned based on a well-documented sense of asymmetric induction expected from \((\text{N-acylated sultam} \ 3)\). We encountered certain difficulties during the cleavage of adduct \((5)\) to \((\text{N-acylation of sultam} \ 2)\) (and recovering chiral auxiliary \((3)\)). An obvious solution would have been base-catalyzed hydrolysis reported for the Diels–Alder adduct of \((\text{N-propenoyl-2,10-camphorsultam} \ 2)\) and butadiene. However, hydrolysis of \((5)\) with lithium hydroxide in aqueous THF 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. Unlike lithium hydroxide, lithium hydroperoxide did hydrolyze adduct \((5)\), but the yields of both \((\text{N-acylated sultam} \ 2)\) and sultam \((3)\) were low. The main product was a water-soluble material identified on the basis of \(^1\)H NMR and IR spectra as sulfonic acid \((6)\), arising from a somewhat unexpected cleavage of the S–N bond. The main evidence from \(^1\)H NMR in favor of structure \((6)\) was a substantial difference in chemical shifts of the magnetically non-equivalent protons in \(^1\)H NMR spectrum. The conversion of \((5)\) to \((\text{N-acylation of sultam} \ 2)\), we used a slightly modified version of a two-step procedure reported by Oppolzer et al. Adduct \((5)\) was first reduced with LAH in THF to give sultam \((3)\) and intermediate \((6)\)-methyl-3-cyclohexenemethanol, and the latter was oxidized in situ with pyridinium dichromate in DMF to give \((2)\). Extractive separation of the products followed by chromatography afforded 71% \((\text{N-acylation of sultam} \ 2)\) 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. and was further improved by recycling the unwanted stereoisomer. Sequential iodolactonization of \((\text{N-acylation of sultam} \ 2)\) and reduction of iodolactone according to published methodology yielded lactone \((7)\). For ring opening of \((7)\), we...
used methyltrichlorosilane/sodium iodide mixture,\(^*\) which appeared to be more efficient than chlorotrimethylsilane/sodium iodide.\(^*\) Initially, acid 8 formed almost exclusively (after hydrolysis of the intermediate silyl ester). Apparently, cleavage of lactone 7 occurs 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 \(\text{Cl}_3\text{SiCH}_3\) (1 equiv.) and \(\text{NaI}\) (3 equiv.) in \(\text{CH}_2\text{CN}\), or just in a solution of \(\text{NaI}\) (2 equiv.) in \(\text{CH}_2\text{CN}\), for 7–8 h resulted in mixtures of 9 and 8 containing 30–40% of the latter.\(^*\) Similarly, ceraleur B1 upon reflux with \(\text{NaI}\) (2 equiv.) in \(\text{CH}_2\text{CN}\) for 12 h gave a mixture of 1 and the \(\text{trans}-3\)-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 \(\text{SN}_2\) type displacement of the existing iodine atom at C-3. The 5-cis-iodo isomer 9 appears to be thermodynamically more stable than the \(\text{trans}\)-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 ceraleur 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 aqueous \(\text{K}_2\text{CO}_3\) (pH 5–6) 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 \(\text{K}_2\text{CO}_3\) (pH ~8–9) and ether/hexane (1:1). Consequently, successive ring opening of lactone 7 and reconvert 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 (trans)-ceralure B1 which was isolated by flash chromatography in 92–94% purity. In the last step, acid 8, reconverting the unwanted acid 9 to (cis)-1 was isolated by flash chromatography and crystallization conveniently removed the 7-cis-epimers 8 isomer 8 from the main product. The overall yield of racemic ceraleur B1 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 (−)-(1R,2R,5R)-7a in 75% yield.\(^*\) Treatment of 7a with \(\text{Cl}_3\text{SiCH}_3/\text{NaI}\) for 2 h followed by recycling of iodoacid 8a using the described protocol afforded (−)-(1R,2R,5R)-iodoacid 9a in 64% yield after crystallization from heptane. Finally, 9a was esterified to (−)-ceralure B1 1a in an overall yield of 46% based on 2a, and 26% based on (−)-borne-10,2-sultam 3.

In summary, a convenient and easily scaleable synthesis of both racemic and (−)-ceraleur B1 was developed. Inasmuch as racemic ceraleur B1 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 x 0.25 mm RTX-1701 column (Restek Corporation) and H2 as a carrier gas. Optical purity of (−)2 was determined on ChiralDEX B-DM GC column (β-cycloextrim, dimethyl). 30 m x 0.25 mm (Advanced Separation Technologies, Inc.). Mass spectra were obtained with a Hewlett-Packard 5971 GC–MS equipped with a 30 m x 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,\(^*\) a two-step transformation to (−)-(camphorsulfonylimine,\(^*\) and reduction with LAH.\(^*\) Mention of a proprietary company or product does not imply endorsement by the US Department of Agriculture.

#### 3.1.1. (−)-N-[((E)-2'-Butenoyl)borne-10,2-sultam (4).\(^*\)

A solution of (−)-borne-10,2-sultam 3 (26.4 g, 0.123 mol), trans-crotonyl chloride (47.3 mL, 0.491 mol) and anhydrous \(\text{CuCl}_2\) (1.64 g, 0.012 mol) in anhydrous benzene (180 mL) was refluxed under \(\text{N}_2\) 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, \(\text{CHCl}_3\)). Lit.\(^*\) mp 186–187°C. \([\alpha]_D=-99.5\) (c 1.04, \(\text{CHCl}_3\)). IR (KBr, cm\(^{-1}\)): 2910, 1680, 1640, 1450, 1380, 1330, 1225, 1135, 975, 880, 780, 760. \(^1\)H NMR (\(\text{CDCl}_3\)): 0.95 (s, 3H), 1.14 (s, 3H), 1.25–1.47 (m, 2H), 1.85–2.20 (m, 5H), 1.90 (dd, \(J_{1,2}=1.5, 15.0\) Hz, 1H), 7.06 (dq, \(J_{2,3}=14.0\) Hz, 1H), 3.48 (1H, d, \(J_{3,4}=14.0\) 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]borne-10,2-sultam (5).

To a dry 250 mL flask equipped with a pressure-equilized dropping funnel, was cannulated a solution of 4 (5.66 g, 20.0 mmol) in anhydrous \(\text{CH}_2\text{Cl}_2\) (43 mL) containing galvinoxyl (0.25 g). The resulting red-brown solution was cooled to ~78°C, and EtAlCl2 (3.2 mL, 30.4 mmol) in anhydrous \(\text{CH}_2\text{Cl}_2\) (10 mL)
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. NaHCO₃ (50 mL) and more brine (50 mL). The solution was dried (MgSO₄), 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, [α]D = −159.3 (c 1.6, CHCl₃). 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 (CDCl₃): 0.95 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H), 1.12 (s, 3H), 1.18–1.45 (m, 2H), 2.27–2.50 (m, 1H), 2.91 (ddd, J₁ = 5.5 Hz, J₂ = J₃ = 10.5 Hz, CH₃), 5.55–5.93 (m, CH = CHH₂CH). Anal. Calcd for C₁₃H₂₅NO₄S: C, 58.76; H, 10.00; N, 3.93. Found: C, 58.65; H, 9.75; N, 3.94.

3.1.3. (−)-(1R,6R)-6-Methyl-3-cyclohexene-1-carboxylic 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 N₂ over a period of 20 min. The reaction mixture was stirred at room temperature for 4 h, then reacted 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 (28 mL) and stirred with pyridinium dichromate (7.62 g, 181–183°C, 86–88°C/0.6 torr, to give 7 (18.91 g) of the product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield 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-methylcyclohexene-1-carboxylic 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 N₂ 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 Na₂SO₄. 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 N₂ 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 K₂CO₃ (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% H₂SO₄, dried with Na₂SO₄, and evaporated to recover starting lactone 7 (1.40 g, 10 mmol, 97% purity). Thus, the conversion after consecutive ring opening and lactonization steps was 60%. 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 Na₂SO₄. Evaporation of the solvent provided a mixture of 32% starting lactone 7, 5% acid 9 and 60% acid 8. The mixture was dissolved in water and treated with 10% K₂CO₃ 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% H₂SO₄ to pH ~2 and extracted with CH₂Cl₂ (4×20 mL). After drying the extract with Na₂SO₄, 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. ¹H NMR (300 MHz, CDCl₃): 1.01 (d, J = 6.5 Hz, CH₃), 1.47–1.85 (m, 5H, CH₃, 2a, 3a, 4a, 5), 2.06 (m, 1H, H-4e), 2.55 (dd, J₆a-₅a = 3.0 Hz, J₆a-₄a = 11.0 Hz, H-1a), 4.84 (m, 1H, H-5e), 11.15 (1H, OH). ¹³C NMR (76 MHz, CDCl₃): 20.1 (CH₃), 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. Twenty. Anal. Calcd for C₈H₁₃IO₂: C, 35.80; H, 4.90. Found: C, 36.09; 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.

3.1.10. (−)-(1R,2R,S,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, 21 mmol). The mixture was refluxed for 2 h. After stirring for 2 h at rt, the mixture was diluted with CH₂Cl₂ (25 mL) and washed with water, 5% HCl, water and dried with Na₂SO₄. Evaporation of the solvent left Crystalline 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 (Rₜ = 0.4, 98% pure). The isolated yield of Crystalline 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%), 165 (15), 123 (10), 95 (100), 81 (12), 67 (22), 55 (25). Continuing elution with the same solvent furnished 30 mg ethyl cis-4-iodo-2-methylcyclohexanecarboxylate (10, Rₜ = 0.3). ¹H NMR (300 MHz, CDCl₃): 0.61 (m, H-3a), 0.69 (d, J = 6.5 Hz, CH₃), 0.80 (m, H-5a), 0.86 (t, J = 6.0 Hz, CH₂CH₃), 2.06 (dm, H-6e), 1.58–1.76 (m, 3H, J = 2.05 (dd, J₆a-₅a = 11.5 Hz, J₆a-₄a = 3.5 Hz, H-5a), 2.32 (m, H-2a), 3.87 (q, CH₂CH₃), 4.16 (m, H-4e), ¹³C NMR (76 MHz, CDCl₃): 14.3 (CH₃CH₂), 19.4 (CH₃), 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 (CH₂CH₃), 174.8 (C═O). ¹³C NMR data were identical to those reported in the literature. Twenty-one.

3.1.11. Ethyl (−)-(1R,2R,S,R)-5-iodo-2-methylcyclohexanecarboxylate (1a). Analogously to the achiral synthesis, 9a (2.23 g, 8.32 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (14 mL) in the presence of pyridine (795 μL) to 1a (2.34 g, 95% yield), [α]D = −33.1 (c 0.80, CH₂Cl₂). Twenty-two. Lit. [α]D = −29.0 (c 0.72, CH₂Cl₂).

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 N₂ 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 Na₂SO₄. Evaporation of the solvent provided a mixture of 32% starting lactone 7, 5% acid 9 and 60% acid 8. The mixture was dissolved in water and treated with 10% K₂CO₃ 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% H₂SO₄ to pH ~2 and extracted with CH₂Cl₂ (4×20 mL). After drying the extract with Na₂SO₄, 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. ¹H NMR (300 MHz, CDCl₃): 1.01 (d, J = 6.5 Hz, CH₃), 1.47–1.85 (m, 5H, CH₃, 2a, 3a, 4a, 5), 2.06 (m, 1H, H-4e), 2.55 (dd, J₆a-₅a = 3.0 Hz, J₆a-₄a = 11.0 Hz, H-1a), 4.84 (m, 1H, H-5e), 11.15 (1H, OH). ¹³C NMR (76 MHz, CDCl₃): 20.1 (CH₃), 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. Twenty. Anal. Calcd for C₈H₁₃IO₂: 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.
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