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Synthesis of (9*E*)-isoambrettolide, a macrocyclic musk compound, using the effective lactonization promoted by symmetric benzoic anhydrides with basic catalysts

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Abstract—Two alternative methods for the synthesis of (9*E*)-isoambrettolide are established via the rapid lactonization of the free *threo*-aleuritic acid or its protected seco-acid using substituted benzoic anhydrides with basic catalysts. The most efficient lactonization of the *threo*-aleuritic acid is performed using 2-methyl-6-nitrobenzoic anhydride (MNBA) with a catalytic amount of 4-dimethylaminopyridine *N*-oxide (DMAPO).

1. Introduction

Macrocyclic compounds, such as (−)-muscone (**1**), the key odorous component of musk, and civetone (**2**), the key odorous component of civet, have a typical animal-like musk odor (Fig. 1).[1,2] From ancient times, musk obtained from the scent gland of the male musk-deer, *Moschus moschiferus*, and civet obtained from the scent glands of the male and female musk-cat, *Viverra civetta* L, had been used for many famous perfumes as the most important fragrance raw material. However, the supply of these rare natural raw materials has recently become extremely short and difficult due to them being on the endangered species list and their unusual breeding methods. Therefore, the development of practical methods for the syntheses of musk compounds, such as (−)-muscone (**1**)[3] and civetone (**2**),[4] is an important subject in perfume chemistry.

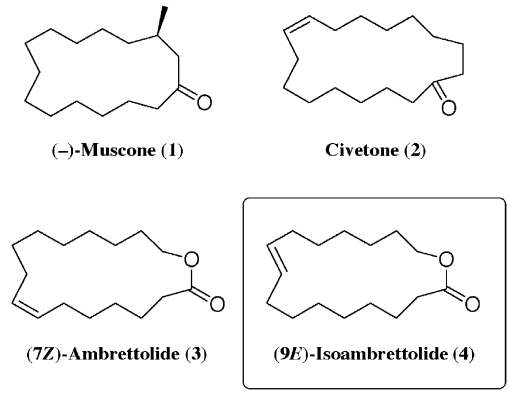

Figure 1. Some macrocyclic perfumed molecules.

On the other hand, some vegetable oils, such as ambrette seed oil, also have a musk-like odor[5] and are frequently used as valuable fragrance raw materials. Interestingly, the odorous key component of the ambrette seed, *Hibiscus abelmochus* L, is a 17-membered ring lactone, (7*Z*)-ambrettolide (**3**),[6] which has an elegant musk odor. Furthermore, (9*E*)-isoambrettolide (**4**) is now a very attractive artificial substrate as an alternative musk resource, and several methods for the synthesis of **4** have been reported.[7–10]

In 1972, Mookherjee reported a protocol for providing macrocyclic lactones involving **4** from cyclohexadeca-l,9-diene via a successive double-epoxidation, non-selective epoxy-opening reduction, Baeyer–Villiger oxidation and dehydration.[7] Although this process gives **4** in only five steps from the starting material, extraction of the desired **4** from the mixture of several isomeric products requires complicated operations and the total yield of the targeted molecule is not sufficient for the industrial production of **4**.

Independently, Bhattacharyya et al.[8] and Tseng[9] developed original methods for the production of **4** starting from

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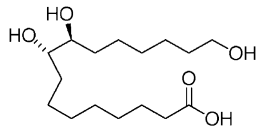


threo-Aleuritic acid (**5**)

Figure 2. *threo*-Aleuritic acid (**5**), a naturally occurring trihydroxycarboxylic acid.

threo-aleuritic acid (**5**, depicted in Fig. 2),[11] a major ingredient of the natural shellac produced by *Laccifer lacca*.

In the former case, **5** was first converted to the corresponding tribromide by the substitution of all the hydroxyl groups. Successive reductive double-bond formation of the vicinal dibromide part, hydroxylation of the resulting primary bromide and saponification of the ester moiety produced the intermediate seco-acid. Finally, the non-chemoselective polymerization of the seco-acid using a traditional dehydration condensation method and distillation of the monomeric lactone from the mixture under depolymerization conditions formed **4** in moderate yield. In the latter one, a dioxolane derivative was first prepared from **5** using acidic transacetalization, and the intermediate was then transformed into the corresponding *cis*-olefin by pyrolysis under severe conditions. Finally, consecutive trans-polymerization and depolymerization procedures at high temperature with potassium hydroxide were repeated several times under reduced pressure to afford the desired monomeric lactone **4** in moderate yield.

Furthermore, Villemin developed an improved method for the preparation of **4** by thermolysis of a mixed *N*,*O*-orthoester generated from **5**, followed by polymerization and depolymerization techniques.[10] In this procedure, the desired monomeric lactone **4** was first obtained in 35% yield from the reaction mixture by distillation, and then 30% of **4** was additionally generated from the polymeric mixture by the second thermo-depolymerizing operation.

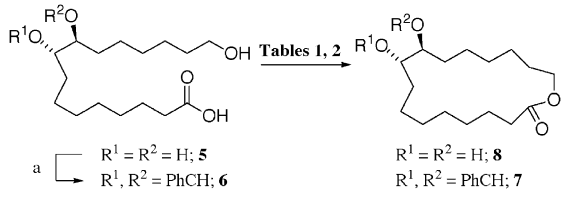
Because very severe conditions and inefficient stepwise procedures were required for the preparation of **4** in the successive polymerization and depolymerization process, it is desirable to develop more effective and facile methods for the synthesis of the monomeric lactone **4** from the corresponding seco-acids.

Recently, we developed a new and rapid lactonization of ω-hydroxycarboxylic acids using symmetric substituted benzoic anhydrides such as 2-methyl-6-nitrobenzoic anhydride (MNBA) as a condensation reagent.[12,3dd] This protocol could be performed by a very simple procedure, and the desired lactones are obtained within a very short time under mild conditions since the reaction quickly proceeds by the promotion of a catalytic amount of basic catalysts such as DMAP or its *N*-oxide (DMAPO). In this paper, we now report a simple method for the synthesis of (9*E*)-isoambrettolide (**4**) from *threo*-aleuritic acid (**5**) using an effective lactonization protocol accelerated by symmetric benzoic anhydrides, as a part of our continuous efforts for the application of the new synthetic methodology to produce useful lactones.[12,13]

2. Results and discussion

2.1. Lactonization of protected seco-acid

The two possible alternative pathways for producing **4** from **5** are as follows (Scheme 1): (i) masking the vicinal dihydroxy unit in **5** with cyclic protective groups, followed by lactonization and successive conversion of the bicyclic compound to the final targeted compound **4**, or (ii) the direct lactonization of trihydroxycarboxylic acid **5** to produce the corresponding dihydroxylactone **8**, a potential intermediate of the lactone **4**, by our effective monomer-selective cyclization using symmetric benzoic anhydrides.



Scheme 1. Reagents and conditions: (a) $PhCH(OMe)_2$, CSA, DMF, 60 °C (66%).

We initially attempted the preparation of the protected lactone **7** via the seco-acid **6** prepared from **5** by treatment with $PhCH(OMe)_2$ and 10-camphorsulfonic acid (CSA). First, optimization of the reaction conditions was carried out for the lactonization of **6** as shown in Table 1. When a solution of **6** in dichloromethane was slowly added to the reaction mixture of 1.2 equiv of MNBA and 2.4 equiv of DMAP in dichloromethane over a 16.5 h period at room temperature, the corresponding monomeric lactone **7** was obtained in 84% yield along with 7% of the dimeric lactide (Entry 1). Further examination to decrease the amount of DMAP to 20 mol% with the use of an excess amount of triethylamine afforded a lower yield of the desired monomer (59%), although the yield of the undesired dimeric compound increased to 21% (Entry 2). On the other hand, when DMAPO, a novel powerful basic catalyst, was employed in Entry 3, the yield of the monomer dramatically increased and reached 77%. The difference between these two reactions indicates that the combination of MNBA and DMAPO is more efficient than that of MNBA and DMAP. Careful monitoring of the reaction mixture by the TLC analysis showed that the rate of the cyclization using DMAPO is apparently faster compared with that using DMAP, therefore, the chemical yields of the lactones and the product-selectivity of the monomer to dimer might be improved in the DMAPO-catalyzed reaction system.

Table 1. Synthesis of 17-membered ring lactone **7** from protected seco-acid **6** using MNBA

Entry	Dehydrating agent	Base	Yield/%	
			Monomer	Dimer
1	MNBA	DMAP (2.4 equiv)	84	7
2	MNBA	DMAP (0.2 equiv), Et_3N (2.2 equiv)	59	21
3	MNBA	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	77	10
4	$(PhCO)_2O$	DMAP (2.4 equiv)	79	10
5	$(PhCO)_2O$	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	60	9

We further examined the effect of the substituents on the aromatic moiety of the symmetric benzoic anhydrides in our mixed anhydride method for the synthesis of lactone **7**. As shown in Entries 4 and 5, the same lactonization of **6** was carried out using the simple benzoic anhydride instead of using MNBA in order to investigate a commercially advanced method for the synthesis of **4**. When the benzoic anhydride was used together with a stoichiometric amount of DMAP for the reaction of **6**, the desired monomeric lactone **7** was obtained in good yield (79%) and the chemoselectivity is similar to the result for Entry 3. From the point of view concerning the economic cost of the dehydrating reagents, the use of cheap benzoic anhydride is also one of the convenient ways to produce the desired compounds in high yields. It is noteworthy that this method seems to be applicable to realize a new industrial production process of the perfume **4**. On the other hand, the catalytic reaction using DMAPO in the presence of the simple benzoic anhydride did not produce a satisfactory yield of **7** (Entry 5).

2.2. Lactonization of non-protected seco-acid and the short-step synthesis of (9*E*)-isoambrettolide

Next, we tried to develop the direct lactonization using *threo*-aleuritic acid (**5**) itself as shown in Table 2. First, the standard reaction conditions (1.2 equiv of MNBA and 2.4 equiv of DMAP) were used for the synthesis of the dihydroxylactone **8**. Since **5** did not completely dissolve in the dichloromethane at room temperature, the entire amount of **5** was added at once to the reaction mixture containing MNBA and DMAP in dichloromethane. By use of this unusual procedure for the chemoselective lactonization, the desired monomeric compound **8** was formed in moderate yield (Entry 1 or 2). Similar results were unfortunately attained using THF as the solvent instead of dichloromethane (Entries 3 and 4), although the solubility of the free carboxylic acid **5** in THF sufficiently increased. Interestingly, the yield of lactone **8** remarkably improved to 77% using the mixed-solvent composed of THF and dichloromethane in the reaction; that is, the starting seco-acid was dissolved in THF prior to use, which was then added to the reaction mixture including MNBA and DMAP in dichloromethane over a 12 h period at room temperature (Entry 5).

Table 2. Synthesis of 17-membered ring lactone **8** from free seco-acid **5** using MNBA

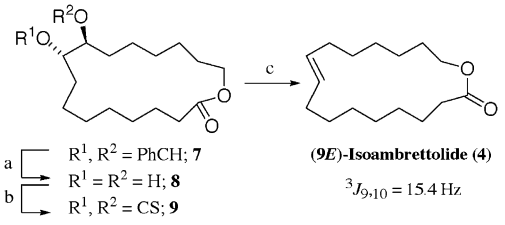
Entry	Base	Solvent	Concn/mM	Method	Yield/%
1	DMAP (2.4 equiv)	CH_2Cl_2	1.8	A[a]	49
2	DMAP (2.4 equiv)	CH_2Cl_2	3.6	A[a]	41
3	DMAP (2.4 equiv)	THF	1.8	A[a]	48
4	DMAP (2.4 equiv)	THF	1.8	B[b]	40
5	DMAP (2.4 equiv)	Mixed[c]	1.9	B[b]	77
6	DMAP (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	67
7	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	83
8	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	CH_2Cl_2	1.8	A[a]	62
9[d]	DMAP (2.4 equiv)	CH_2Cl_2	1.8	A[a]	40
10[d]	DMAP (2.4 equiv)	Mixed[c]	1.9	B[b]	69
11[d]	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	50

[a] Method A: solid **5** was added at once to a solution of reagents.
[b] Method B: A solution of **5** was slowly added to a solution of reagents.
[c] A solution of **5** in THF was added to a solution of reagents in CH_2Cl_2.
[d] Benzoic anhydride was used as a dehydrating agent instead of MNBA.

Based on these results, the reaction was then carried out with 20 mol% of DMAPO and an excess amount of triethylamine in the mixed-solvent at room temperature, and the yield of **8** finally reached 83% as shown in Entry 7. Although we have tried to apply DMAP as a catalyst to this reaction system as shown in Entry 6, the yield of the monomer decreased to 67%. The difference between the yields for Entries 6 and 7 again shows that DMAPO is superior to DMAP for the generation of the desired monomeric lactones in the MNBA cyclization.

Next, a simple benzoic anhydride was used instead of MNBA for the cyclization of the free *threo*-aleuritic acid (**5**). The desired compound was obtained in 40% yield when the reaction was carried out by the total addition of the solid starting material to the solution of promoters (Entry 9), however, the yield increased to 69% by the slow-addition of a solution of the seco-acid in THF to a solution of promoters in dichloromethane (Entry 10). It is also showed that the combination of simple benzoic anhydride and DMAPO as a dehydrating reagent and as a basic catalyst, respectively, is ineffective for the reaction of the free seco-acid **5** (Entry 11) even though the couple of MNBA and DMAPO is an universally suitable combination of the promoters (Entry 7).

The facile deprotection of **7** with $AcOH/H_2O$ was then carried out to produce the *threo*-aleuritic acid lactone (**8**), which is an important synthetic intermediate (9*E*)-isoambrettolide (**4**) as depicted in Scheme 2. The dihydroxylactone **8** prepared by the above-mentioned two methods was in turn converted to the corresponding thiocarbonate **9** by treating with 1,1′-thiocarbonyldiimidazole (TCDI) and DMAP under reflux in toluene. Finally, it was transformed into (9*E*)-isoambrettolide (**4**) using trimethyl phosphite in 87% yield.[14] The geometric structure of **4** was determined from the coupling constants data of olefinic protons using ^1H NMR.



Scheme 2. Reagents and conditions: (a) AcOH, H_2O, rt (93%); (b) TCDI, DMAP, toluene, 130 °C (91%) and (c) $P(OMe)_3$, 140 °C (87%).

2.3. Conclusion

Thus, the substituted benzoic anhydride method was successfully used for the formation of the large-ring lactones having some oxygenated functionalities, which are useful synthetic intermediates of (9*E*)-isoambrettolide (**4**). Through this synthetic study, the protected or unprotected 17-membered ring lactone (**7** or **8**) was consequently prepared from the corresponding masked or free seco-acid (**6** or **5**) using MNBA as the dehydrating reagent with DMAPO, a powerful

basic catalyst. In particular, we revealed that the latter pathway is extremely efficient for the preparation of the synthetic intermediates of **4** since only three steps (83%, 91%, and 87% yields, respectively) are required to produce the artificial perfume compound **4** starting from **5**.

On the other hand, the combination of a simple benzoic anhydride and commercially available DMAP is practically useful for the industrial supply of **4** since inexpensive reagents and facile protocols are employed in this synthetic strategy. Therefore, it is also revealed that the intramolecular dehydration method using symmetric benzoic anhydrides with basic catalysts could be applicable for the plant-scale production of the musk-like lactones as well as the synthesis of other complicated molecules such as multi-oxygenated large- or medium-sized ring lactones.[12]

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-S3 micro-melting point apparatus. IR spectra were recorded on a Horiba FT-300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-AL300 or a JEOL JNM-LA500 spectrometer with cholorform (in chloroform-*d*) or benzene (in benzene-d_6) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F.

All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, tolune and DMF were distilled from diphosphrous pentoxide, and dried over MS 4 Å, and THF was distilled from sodium/benzophenone immediately prior to use. *threo*-Aleuritic acid (**5**) was purchased from Fulka Chemical Co., Ltd, and used after purification by silica gel chromatography (eluant; chloroform/methanol = 10/1). 2-Methyl-6-nitrobenzoic anhydride (MNBA) was purchased from Tokyo Kasei Kogyo Co., Ltd (TCI, M1439). Other reagents were purchased from Tokyo Kasei Kogyo Co., Ltd, Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted.

3.2. *threo*-9,10-Benzylidenedioxy-16-hydroxyhexadecanoic acid (6)

To a solution of *threo*-aleuritic acid (**5**) (222 mg, 0.729 mmol) and benzaldehyde dimethylacetal (0.120 mL, 0.800 mmol) in DMF (0.73 mL) at room temperature was added CSA (33.8 mg, 0.146 mmol). After the reaction mixture had been stirred for 5 h at 60 °C and for 10 h at room temperature, triethylamine (0.02 mL) was added. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by column chromatography (eluant; dichloromethane/methanol = 20/1) to afford benzylidene acetal **6** (a mixture of stereoisomeric benzylidene acetals, ca. 1:1, 190 mg, 66%) as a colorless oil. IR (neat): 3420, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.51–7.43 (m, 2H, Ph), 7.41–7.31 (m, 3H, Ph), 5.86 (s, 1H, CHPh), 3.81–3.71 (m, 2H, 9-H, 10-H), 3.65 (t, J=6.2 Hz, 2H, 16-H), 2.34 (t, J=7.0 Hz, 2H, 2-H), 1.74–1.23 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR (C_6D_6): δ 179.4 (1), 139.6 (Ph), 129.1 (Ph), 128.4 (Ph), 127.1 (Ph), 103.0 (CHPh), [83.0, 83.0] (9 or 10), [81.7, 81.6] (10 or 9), 62.6 (16), [34.4, 34.3] (2), 33.3, 33.3, 32.8, [29.7, 29.7], [29.7, 29.6], [29.4, 29.4], 29.2, [26.5, 26.4], [26.3, 26.3], [26.0, 26.0], 25.1 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). The values in square brackets are the chemical shifts of the identical carbons of two diastereomers. HRMS: calcd for $C_{23}H_{37}O_5$ (M+H$^+$) 393.2641, found 393.2632.

3.3. *threo*-9,10-Benzylidenedioxyheptadecan-16-olide (7)

An experimental procedure is described for the preparation of lactone **7** using MNBA with a catalytic amount of DMAPO (Table 1, Entry 3). To a solution of MNBA (116 mg, 0.337 mmol), triethylamine (62.8 mg, 0.621 mmol), and DMAPO (7.7 mg, 0.056 mmol) in dichloromethane (116 mL) at room temperature was slowly added a solution of benzylidene acetal **6** (110 mg, 0.280 mmol) in dichloromethane (84 mL) with a mechanically driven syringe over a 16.5 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford lactone **7** (a mixture of stereoisomeric benzylidene acetals, ca. 1:1, 77.0 mg, 77%) as a white solid and its dimer (10.3 mg, 10%) as a pale yellow oil. **7**: IR (KBr): 1730 cm^{-1}; ^{1}H NMR (C_6D_6): δ 7.67–7.61 (m, 2H, Ph), 7.23–7.10 (m, 3H, Ph), 5.97 (s, 1H, CHPh), 4.07–3.93 (m, 2H, 16-H), 3.81–3.66 (m, 2H, 9-H, 10-H), 2.22–2.06 (m, 2H, 2-H), 1.88–0.97 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR (C_6D_6): δ 172.9 (1), 139.6 (Ph), 129.1 (Ph), 128.4 (Ph), 127.1 (Ph), [102.9, 102.8] (CHPh), [82.3, 82.2] (9 or 10), [80.8, 80.7] (10 or 9), 63.9 (16), 34.5 (2), [33.3, 33.1], 32.4, 29.1, 28.8, [28.7, 28.6], 28.3, 27.8, [25.9, 25.8], [25.5, 25.2], [25.0, 24.9], 24.3 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). The values in square brackets are the chemical shifts of the identical carbons of two diastereomers. HRMS: calcd for $C_{23}H_{35}O_4$ (M+H$^+$) 375.2535, found 375.2532.

3.4. *threo*-9,10-Dihydroxyheptadecan-16-olide (8)

3.4.1. From 7. To lactone **7** (9.9 mg, 0.026 mmol) at room temperature were added acetic acid (0.76 mL) and water (0.19 mL). After the reaction mixture had been stirred for 24 h at room temperature, saturated aqueous sodium hydrogencarbonate and solid sodium hydrogencarbonate were successively added at 0 °C. The reaction mixture was stirred for 10 h and then the mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford dihydroxylactone **8** (7.0 mg, 93%) as a white solid. Mp 53.5–54.0 °C; IR (KBr): 3440, 3310, 1730 cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 4.18–4.05 (m, 2H, 16-H), 3.50–3.41 (br m, 2H, 9-H, 10-H), 2.40 (br s, 2H,

9-OH, 10-OH), 2.31 (t, J=6.8 Hz, 2H, 2-H), 1.70–1.22 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDC1_3$): δ 174.0 (1), 74.1 (9 or 10), 73.4 (10 or 9), 64.2 (16), 34.6 (2), 32.5, 31.4, 28.6, 28.2, 28.1, 27.7, 27.6, 25.4, 25.0, 23.9, 23.1 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15); Anal. calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.97; H, 10.54. HRMS: calcd for $C_{16}H_{31}O_4$ ($M+H^+$) 287.2222, found 287.2223.

3.4.2. From 5; direct lactonization of *threo*-aleuritic acid. An experimental procedure is described for the preparation of dihydroxylactone **8** using MNBA with a catalytic amount of DMAPO (Table 2, Entry 7). To a solution of MNBA (165 mg, 0.479 mmol), triethylamine (89.1 mg, 0.881 mmol), and DMAPO (11.1 mg, 0.080 mmol) in dichloromethane (169 mL) at room temperature was slowly added a solution of **5** (118 mg, 0.388 mmol) in THF (40 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford dihydroxylactone **8** (92.0 mg, 83%) as a white solid.

3.5. *threo*-9,10-Thiocarbonyldioxyheptadecan-16-olide (9)

To a solution of dihydroxylactone **8** (80.2 mg, 0.280 mmol) in toluene (14 mL) were added TCDI (499 mg, 2.80 mmol) and DMAP (3.4 mg, 0.028 mmol). After the reaction mixture had been stirred for 4 h at 130 °C, it was cooled down to room temperature. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford thiocarbonate **9** (83.8 mg, 91%) as a white solid. Mp 73–74 °C; IR (KBr): 1720, 1280, 1180 cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 4.55–4.43 (m, 2H, 9-H, 10-H), 4.21–4.08 (m, 2H, 16-H), 2.42–2.25 (m, 2H, 2-H), 2.10–1.21 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDC1_3$): δ 191.4 (CS), 173.7 (1), 86.1 (9), 86.1 (10), 63.9 (16), 34.4 (2), 32.4, 32.1, 28.7, 28.3, 27.9, 27.9, 27.1, 25.6, 25.0, 23.6, 23.2 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). Anal. calcd for $C_{17}H_{28}O_4S$: C, 62.16; H, 8.59. Found: C, 62.05; H, 8.61. HRMS: calcd for $C_{17}H_{29}O_4S$ ($M+H^+$) 329.1786, found 329.1791.

3.6. (9*E*)-Isoambrettolide (4)

To thiocarbonate **9** (20.4 mg, 0.062 mmol) was added trimethyl phosphite (3 mL) at room temperature. After the reaction mixture had been stirred for 25 h at 140 °C, it was cooled down to room temperature. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford (9*E*)-isoambrettolide (**4**) (13.7 mg, 87%) as a colorless oil. IR (neat): 1730 cm^{-1}; ^{1}H NMR (C_6D_6): δ 5.42 (dddd, J=15.4, 9.5, 3.5, 1.6 Hz, 1H, 9-H or 10-H), 5.32 (dddd, J=15.4, 9.5, 3.8, 1.6 Hz, 1H, 10-H or 9-H), 4.08 (t, J=5.4 Hz, 2H, 16-H), 2.19 (t, J=7.0 Hz, 2H, 2-H), 2.12–1.97 (m, 4H, 8-H, 11-H), 1.62–1.50 (m, 2H, 3-H), 1.48–1.34 (m, 2H, 15-H), 1.42–1.13 (m, 14H, 4, 5, 6, 7, 12, 13, 14-H); ^{13}C NMR (C_6D_6): δ 172.9 (1), 131.4 (9 or 10), 130.8 (10 or 9), 64.0 (16), 34.9 (2), 32.2 (8 or 11), 31.8 (11 or 8), 29.2 (15), 29.9, 28.8, 28.3, 28.2, 28.1, 27.2, 27.1 (4, 5, 6, 7, 12, 13, 14), 25.3 (3). HRMS: calcd for $C_{16}H_{29}O_2$ ($M+H^+$) 253.2167, found 253.2165.

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