Synthetic Routes towards Cryptophycin Unit A Diastereomers

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Abstract: Unit A of cryptophycin 1 is a δ-hydroxy acid with four stereogenic centres. Our unit A synthesis introduces the first two stereogenic centres by a catalytic, asymmetric dihydroxylation, whereas the remaining two stereogenic centres are established by diastereoselective reactions. In this letter, we focus on the diastereoselectivity of these reactions and discuss the accessibility of cryptophycin unit A diastereomers.

Key words: diastereoselectivity, addition reactions, oxidations, cuprates, natural products

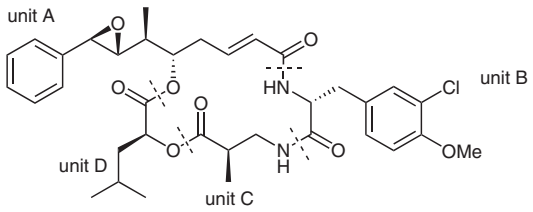
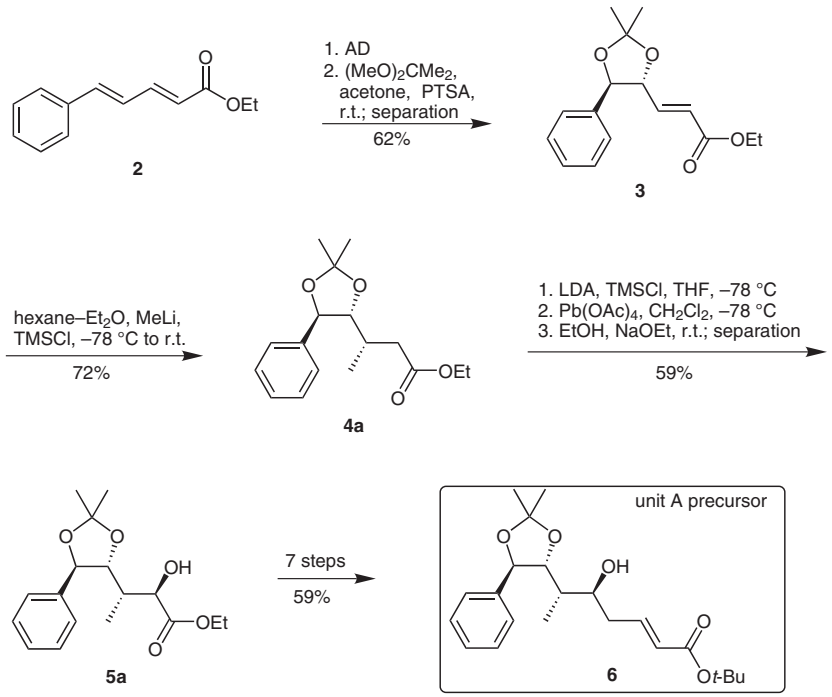


Figure 1 Structure of cryptophycin 1 (**1**)

The cryptophycins are a family of sixteen-membered macrocyclic depsipeptides isolated from blue-green algae of the genus *Nostoc*.[1] Cryptophycin 1 (**1**) as well as a number of related analogues attracted attention due to their potent antitumour activity which surpasses the activity of agents such as vinblastine and paclitaxel by up to three orders of magnitude. Furthermore, biological activity is often maintained for multidrug-resistant tumour cell lines.[2] Retrosynthetically, cryptophycins can be divided into the respective hydroxy and amino acid building blocks, i.e. units A–D (Figure 1). The synthesis of unit A with four stereogenic centres stands in the focus of many publications on cryptophycin syntheses. In all syntheses of cryptophycin unit-A precursors with four stereogenic centres, the configuration of the future epoxide is established by means of a *syn*-diol, which later in the synthesis is transformed into the epoxide functionality by a three-step reaction sequence with net retention of configuration.[3]

We recently published a thirteen-step[3e] and a seven-step[3f] unit A synthesis (Scheme 1). The former starts with dienoate **2**, which is transformed by an asymmetric dihydroxylation into a mixture of the regioisomeric diols,



Scheme 1 Synthesis of cryptophycin unit A precursor **6**[3e]

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Table 1 Reaction Conditions Leading to Diastereomeric Intermediates of the Cryptophycin Unit A Synthesis

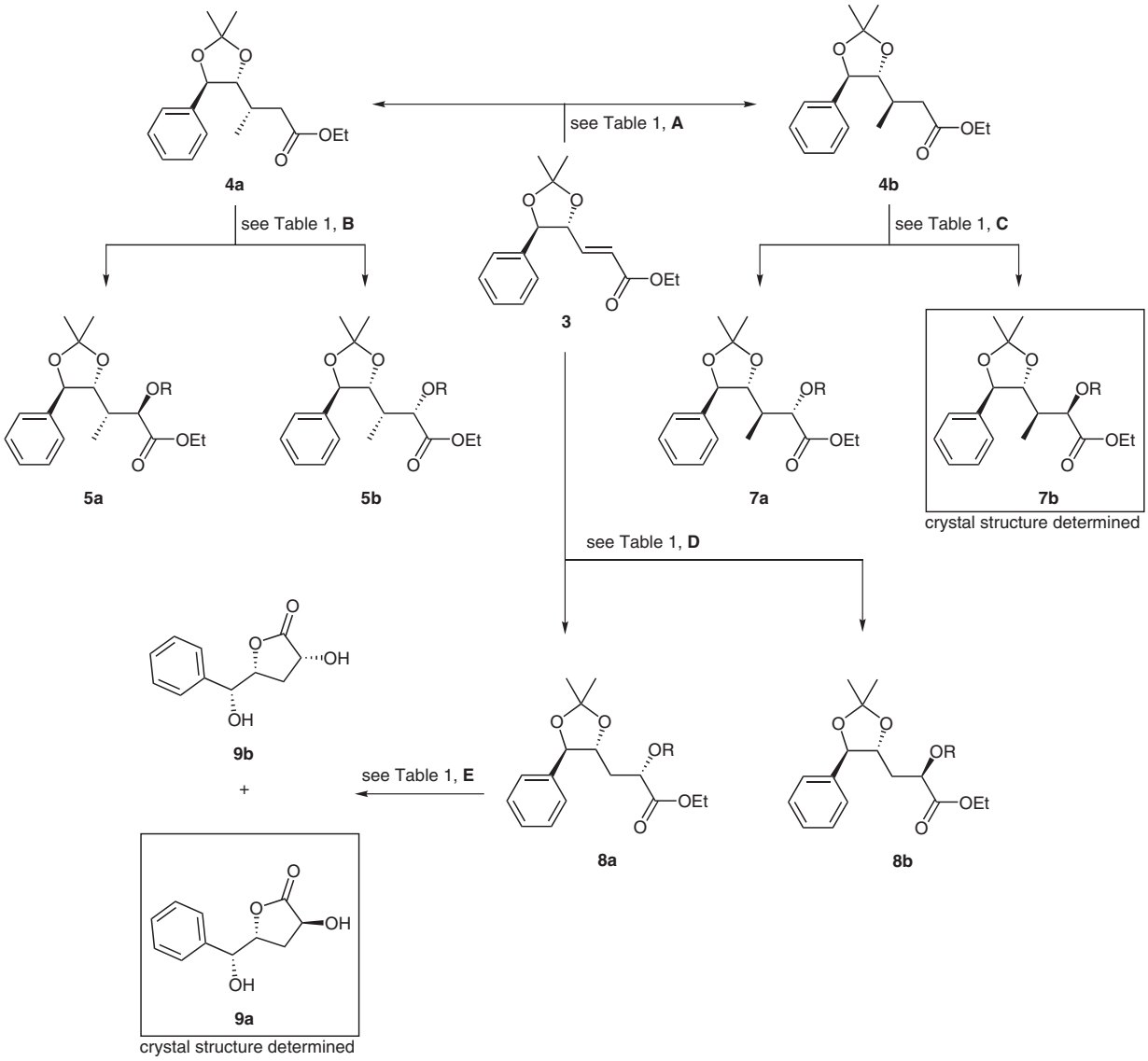
	Entry	Conditions	R	Products		Ratio a/b[a]		Yield (%)
A	1	hexane–Et_2O (4:1), MeLi, TMSCl, –90 °C to –80 °C[4]	–	**4a**	**4b**	99	1	69[b]
	2	Me_2CuLi, TMSCl, Et_2O, –78 °C[4]	–	**4a**	**4b**	14	86	72[b]
	3	Me_2CuLi·LiCN, BF_3·OEt_2, Et_2O, –50 °C	–	**4a**	**4b**	3	97	(44)[c,e]
	4	MeCu·LiI, BF_3·OEt_2, toluene–Et_2O, –78 °C	–	**4a**	**4b**	4	96	52[b]
B	5	1. LDA, TMSCl, THF, –78 °C to r.t. 2. CH_2Cl_2, $Pb(OAc)_4$, –78 °C to r.t. 3. LiOH[3e]	H	**5a**	**5b**	92	8	59[b]
	6	1. LDA, THF 2. MoOPH, –78 °C to r.t.	H	**5a**	**5b**	18	82	59[b]
	7	NaHMDS, THF, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, –78 °C	H	**5a**	**5b**	28	72	(99)[b,d]
C	8	1. LDA, TMSCl, THF 2. CH_2Cl_2, $Pb(OAc)_4$, –78 °C to r.t.	Ac	**7a**	**7b**	50	50	80[b]
	9	LDA, THF, MoOPH, –78 °C to r.t.	H	**7a**	**7b**	33	67	71[b]
		after crystallisation from *n*-hexane	H	**7a**	**7b**	3	97	41[b]
	10	NaHMDS, THF, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, –78 °C	H	**7a**	**7b**	11	89	(82)[b,d]
		after crystallisation from *n*-hexane	H	**7a**	**7b**	6	94	(50)[b,d]
	11	1. NaHMDS, THF, –78 °C 2. (+)-camphorsulfonyloxaziridine, –78 °C	H	**7a**	**7b**	7	93	(31)[b,d,e]
	12	1. NaHMDS, THF, –78 °C 2. (–)-camphorsulfonyloxaziridine, –78 °C	H	**7a**	**7b**	7	93	31[b,e]
D	13	1. H_2, Pd/C 2. LDA, TMSCl, THF, –78 °C to r.t. 3. CH_2Cl_2, $Pb(OAc)_4$, –78 °C to r.t.	Ac	**8a**	**8b**	78	22	62[b]
	14	1. NaHMDS, THF, –78 °C 2. MoOPH, –78 °C to r.t.		**8a**	**8b**	45	55	41[b,e]
E	15	TFA, H_2O, MeCN, r.t.	–	**9a**	**9b**	78	22	93[b]

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield of diastereomeric mixture.
[c] Conversion (FID-GC).
[d] Impurities.
[e] Incomplete conversion.

which after protection as the acetonides is separated by chromatography, and pure regioisomer **3** is obtained. Conjugate addition of methyllithium gives diastereomer **4a** selectively. The α-hydroxy group is introduced in a three-step reaction sequence. The trimethylsilylketene acetal of **4a** is treated with lead(IV)acetate providing the corresponding α-acetoxy compound. Then the newly formed acetate is saponified yielding α-hydroxy acid **5a**, which is further converted into unit A precursor **6** in seven steps.

We already described the selectivity of the conjugate addition to **3**[4] and took this as the starting point for some methodological studies. The results are summarised in Table 1. While the 1,4-addition of methyllithium to **3** selectively gives the 3*S*-configured diastereomer **4a** (Table 1, entry 1), various methylcopper reagents selectively give the 3*R*-configured compound **4b**[5] (entries 2–4). Within the methyl cuprate series, a severe separation problem results from either moderate diastereoselectivity (entry 2) or incomplete turnover (entry 3). After changing to organocopper reagent MeCu·LiI, BF_3·OEt_2[6] (entry 4), and toluene as solvent, we achieved complete conversion and excellent diastereoselectivity at –78 °C.

While addition of methyllithium (Table 1, entry 1) takes place under nonpolar reaction conditions favouring chelate control of reagent approach, there is usually no such influence on diastereoselectivity for cuprate reagents.[7] Nevertheless, there is no comprehensive explanation for the observed diastereoselectivities. The adaptation of the Felkin–Anh model[8] to α,β-unsaturated esters predicts the wrong configuration for either nucleophile (Figure 2, **A**). The Yamamoto model[7a] correctly predicts the configura-



Scheme 2 Diastereoselective transformations of **3** leading to **5a/5b**, **7a/7b** and **8a/8b**, respectively (for reaction conditions, see Table 1)

tion for the methyl cuprate addition, but cannot explain the different stereochemical outcome of the methyllithium addition (Figure 2, **B**). A modified Felkin–Anh model[8] with the smallest substituent pointing towards the same direction as the α,β-unsaturated ester would predict the correct stereochemistry for both the methyllithium and the methyl cuprate addition, but requires the nucleophile to tolerate steric hindrance along the trajectory (Figure 2, **C**). In our opinion, the Yamamoto model gives the best description for organocopper reagents. As to the methyllithium addition, we believe that the modified Felkin–Anh model gives the best rationale because the chelation-controlled approach would put the steric hindrance along the trajectory into perspective.

The stereoselective introduction of the α-hydroxyl group by electrophilic acetoxylation or hydroxylation is straightforward in case of diastereomer **4a** and effectively gives either diastereomer **5a** or **5b** (Table 1, entries 5–7).[3e] The basis for diastereoselectivity is the same in both cases. The initial attack from the least hindered side leads to the final product **5b** in case of MoOPH (entry 6) or oxaziridine oxidation (entry 7). With lead(IV) acetate (entry 5), a cyclic plumbonium ion intermediate is initially formed by addition of $Pb(OAc)_3^+$ to the silylketene acetal double bond from the least-hindered side,[10] and opened by the rear attack of an acetate ion at the α-carbon atom leading to the oppositely configured α-acetoxy compound, which after saponification leads to the corresponding α-hydroxy derivative. Oxidation with racemic 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine occurs in good yield and with a slightly lower diastereoselectivity than MoOPH oxidation (entry 7). A disadvantage using oxaziridines is the occurrence of side products, which are not always readily removed by chromatography.

In the case of diastereomer **4b**, oxidation with MoOPH predominantly gives *syn*-configured isomer **7b** with only low selectivity (entry 9), whereas oxidation of the

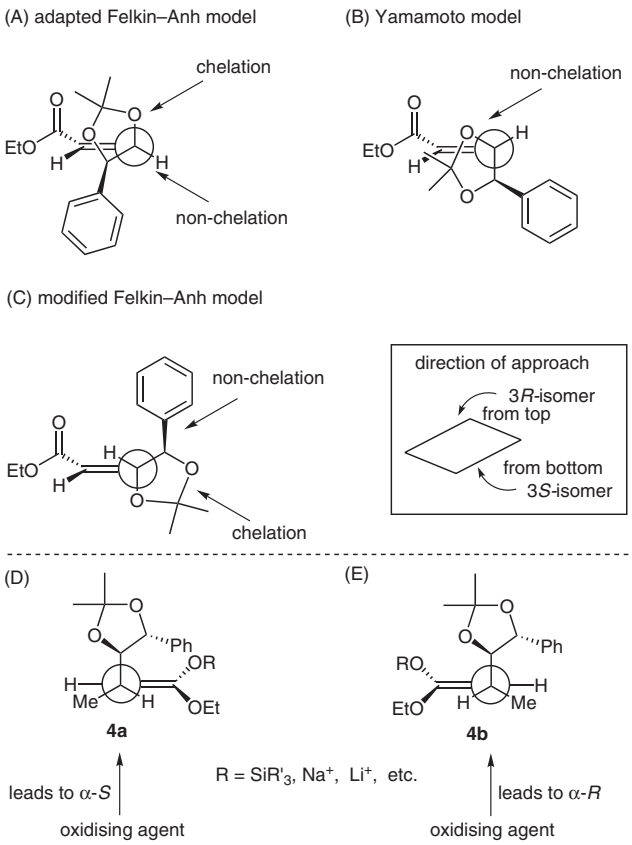


Figure 2 Models for the observed diastereoselectivities of the conjugate addition and the oxidation with MoOPH, oxaziridine-derived reagents, and lead(IV) acetate. A fourth model for the conjugate addition has been suggested by Leonard et al.[9] and is similar to **B** while none of the residues is in exact *anti*-alignment to the enoate double bond, but the alkoxy group is parallel to the enoate double bond.

trimethylsilylketene acetal with lead(IV) acetate is not diastereoselective at all (entry 8). A good *syn*/*anti* selectivity of 9:1 is observed for oxidation with racemic 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (entry 10), i.e. here the oxaziridine oxidation is much more diastereoselective than the oxidation with MoOPH. Interestingly, both chiral oxidising agents (+)-camphorsulfonyloxaziridine (entry 11) and (–)-camphorsulfonyloxaziridine (entry 12) give **7b** with the same excellent diastereoselectivity albeit in low yield at –78 °C. These results indicate that the bulkiness of the reagent significantly hampers the reaction at low temperatures, and that there is no matched/mismatched-pair relationship of the respective transition states under these reaction conditions.

The oxaziridine-derived reagents and MoOPH give the *syn*-configured compound in various degrees of selectivity. Similar selectivity has been observed by Hanessian et al. in the synthesis of polypropionate building blocks of rifamycin S with racemic 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine,[11] and Morizawa et al. in the hydroxylation of β-trifluoromethyl ester enolates with MoOPH.[12] The respective transition-state model (Figure 2, **D** and **E**) emphasises the importance of the neighbouring methyl substituent, which is the main though not the only influence, as indicated by the higher selectivity for the MoOPH oxidation with **4a** and the oxaziridine oxidation with **4b** (Table 1, entry 6, 10). For the oxidation with lead(IV) acetate, there seems to be an additional, decisive influence of the neighbouring dioxolane moiety, because **4a** reacts with high diastereoselectivity whereas **4b** reacts without any diastereoselectivity at all.

The actual influence of the neighbouring methyl substituent on the electrophilic acetoxylation and hydroxylation was examined for the corresponding demethyl compounds. A moderate 3.5:1 selectivity in favour of the *S*-configured diastereomer **8a** is obtained for the lead(IV)acetate oxidation of the corresponding silyl ketene acetal (Table 1, entry 13). Instead, **4a** gives the *R*-configured diastereomer **5a** with a higher diastereoselectivity of 9:1 whereas **4b** gives no diastereoselectivity at all. The oxidation with MoOPH gives the *R*-configured diastereomer **8b** with low diastereoselectivity (1.2:1; Table 1, entry 14) Under these conditions **4a** gives the *S*-configured compound **5b** with a moderate diastereoselectivity of 4:1 whereas **4b** gives the *R*-configured compound **7b** with a moderate diastereoselectivity of 2:1. Consequently, for the lead(IV) acetate oxidation the presence of a β-methyl group with *S*-configuration at the adjacent carbon leads to both an increase and reversion of diastereoselectivity, whereas a corresponding methyl group with *R*-configuration at the adjacent carbon leads to a complete loss of diastereoselectivity. With MoOPH, there is hardly any diastereoselectivity in the absence of a neighbouring methyl group, whereas in its presence diastereoselectivity improves.

In summary, the diastereomers **5a/b** and **7b**[13] were obtained in synthetically useful amounts and purity. The relative configuration of **5a/b** had already been proven,[4] while the relative configuration of **7b** was confirmed by crystal structure analysis.[14] The relative configuration of **8a/8b** was proven by crystal structure analysis of **9a**,[14] which was obtained epimerisation-free from the main diastereomer of a 3.5:1 mixture of **8a/8b** (Table 1, entry 15, diastereomers virtual inseparable). A direct access to pure diastereomer **7a** does not exist since the lead(IV) acetate oxidation failed to be diastereoselective in case of **4b**. Both enantiomers of **3** are accessible depending on the ligand of the asymmetric dihydroxylation, and so are the enantiomers of **5a/b** and **7b**.

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(5) **Synthesis of 4b**
Copper(I) iodide (25.34 mmol, 4.826 g) was dried for 2 h in high vacuum at 100 °C, deoxygenated three times with argon and suspended in anhyd toluene (52 mL). The mixture was cooled to –78 °C, then MeLi (1.4 M) in Et_2O (18.1 mL) was added over 20 min. While the reaction mixture was warmed to –40 °C for 15 min, the suspension turned bright yellow. The mixture was cooled to –78 °C again and $BF_3{\cdot}OEt_2$ (25.2 mmol, 3.58 g, 3.10 mL) was added dropwise and the mixture was stirred for 15 min at –78 °C. Then a solution of (*E*)-ethyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]acrylate (**3**, 7.24 mmol, 2.000 g) in anhyd toluene (5 mL) was added dropwise and after the addition was complete, the reaction mixture was stirred for 16 h at –78 °C. A 9:1 mixture of aq NH_4Cl solution and 25% aq NH_4OH solution (6 mL) was added over 30 min at –78 °C, and the cooling bath was removed. Then, H_2O (50 mL) and hexane (200 mL) were added to the reaction, and the mixture was filtered through a pad of Celite®. The layers of the filtrate were separated, the aqueous phase was extracted three times with hexane (50 mL) and the combined organic layers were washed with sat. NaCl solution (30 mL) and dried over Na_2SO_4. The solvent was removed under vacuum (50 °C). The crude product was purified by flash chromatography (hexane–EtOAc, 12:1) yielding (*R*)-ethyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]butanoate (**4b**, 1.106 g, 52%, 92% de) as a slightly yellow, highly viscous oil. For the analytical data see ref. 4.

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(13) **Synthesis of 7b**: NaHMDS (2 M, 0.68 mmol, 0.34 mL) in THF (2.14 mL) was cooled to –78 °C, then a solution of (*R*)-ethyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]butanoate (**4b**, 0.68 mmol, 0.200 g) in anhyd THF (1.6 mL) was added over 15 min and the mixture was stirred at –78 °C over 75 min. Then, racemic 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (0.95 mmol, 0.248 g,) in anhyd THF (1.6 mL) was added over 15 min and the mixture stirred at –78 °C until the reaction was complete (approx. 1 h). Then, sat. NH_4Cl solution (1.5 mL) was added over 15 min at –78 °C and the mixture allowed to reach r.t. Afterwards, Et_2O (50 mL) and H_2O (10 mL) were added, the layers separated and the aqueous layer extracted three times with Et_2O (50 mL). The combined organic layers were washed twice with H_2O (25 mL) and sat. NaCl solution (25 mL), dried over Na_2SO_4, and the solvent was evaporated under vacuum. The residue was purified twice by chromatography (silica gel 60, hexane–EtOAc, 4:1) to obtain reasonably pure (2*R*,3*R*)-ethyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2-hydroxybutanoate (**7b**, 0.56 mmol, 0.173 g, 82% yield, 77% de). Crystallisation from *n*-hexane gives a diastereomerically enriched material (0.104 g, 0.34 mmol, 50%, 88% de); $[\alpha]_D^{22}$ –4.44 (*c* 1.1, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.45 (m, 5 H), 4.73 (d, *J* = 8.1 Hz, 1 H), 4.61 (dd, *J* = 5.0, 2.2 Hz, 1 H), 4.27 (m, 2 H), 4.02 (dd, *J* = 8.4, 8.4 Hz, 1 H), 2.94 (d, *J* = 5.0 Hz, 1 H), 2.24 (qdd, *J* = 8.7, 6.9, 1.9 Hz, 1 H), 1.56 (s, 3 H), 1.51 (s, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 0.59 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174,5, 138.3, 128.6, 128.5, 127.9, 109.0, 83.5, 83.2, 71.2, 61.7, 40.2, 27.4, 27.3, 14.3, 10.2. IR (neat): 3437, 3065, 3029, 2983, 2933, 2902, 1729, 1496, 1456, 1383, 1306, 1248, 1225, 1173, 1156, 1132, 1096, 1053, 1034, 924, 880, 814, 754, 697. ESI-MS: *m/z* calcd for $C_{17}H_{24}O_5Na^+$: 331.15 $[M + Na]^+$; found: 331.0; *m/z* calcd for $C_{34}H_{48}O_{10}Na^+$ 639.31 $[2\ M + Na]^+$; found: 638.7.

(14) CCDC 668175 (**7b**) and 668176 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.