Zuschriften

## A Catalytic Asymmetric Three-Component 1,4-Addition/Aldol Reaction: Enantioselective Synthesis of the Spirocyclic System of Vannusal A**

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The advantages of multicomponent reactions over the more common two-component processes have been widely demonstrated and reviewed.[1] Efficient asymmetric versions of such reactions offer even greater benefits to the art of chemical synthesis, as these can provide expedient access to polyfunctionalized molecules in enantioenriched form, starting from simple prochiral building blocks.[2,3] During a program directed towards the total synthesis of vannusal A (**1**, Scheme 1), an architecturally complex marine natural product isolated from the ciliate *Euplotes vannus*,[4] the key optically enriched spirocyclic intermediate **2** was required. This demand led us to the development of an asymmetric multicomponent reaction that combined α,β-unsaturated

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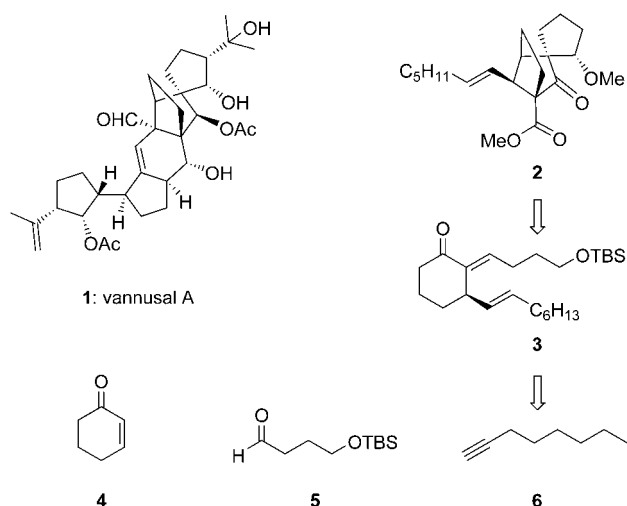
Scheme 1. Stucture of vannusal A (**1**) and retrosynthetic analysis of spirocyclic building block **2**.

enones, aldehydes, and alkenyl zirconium species in the presence of a chiral rhodium catalyst to give enantioselective access to 2,3-disubstituted cycloalkanones. Herein we report this new synthetic technology and describe its application to the construction of enantioenriched building block **2**, which represents the spiro domain of vannusal A (**1**).

Scheme 2 shows the general strategy for the intended three-component (**I**, **II**, and **III**) catalytic asymmetric con-
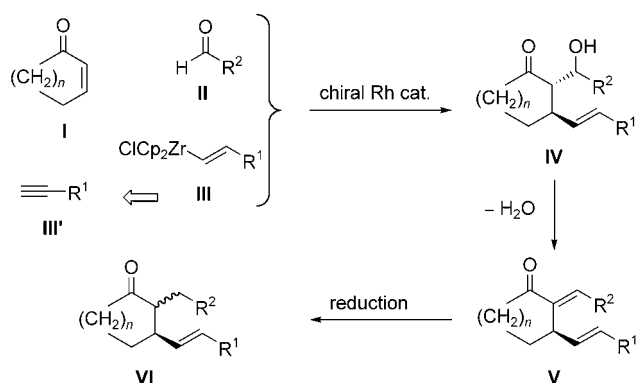

Scheme 2. General scheme for the catalytic asymmetric three-component reaction (**I** + **II** + **III**→**IV**→**V**→**VI**).

struction of aldol-type compounds **IV**, α,β-unsaturated enones of type **V**, and 2,3-disubstituted cyclic ketones of type **VI**. This proposed multicomponent reaction was partially based on the pioneering work of Oi, Sato, and Inoue,[5] who demonstrated the efficient rhodium-catalyzed addition of alkenyl zirconium species to enones (under non-aqueous conditions) to afford 1,4-adducts. Furthermore, the elegant studies of the Hayashi group[6] on the catalytic cycle of the rhodium-catalyzed conjugate addition of *B*-aryl-9-BBN to a reactive vinyl ketone, which showed that a transient rhodium enolate can react with electrophiles, were key to this proposal. Both studies, however, stopped short of a three-component

process capable of delivering enantiomerically enriched products as reported herein. According to our plan, a chiral rhodium complex was to act as a catalyst to induce the asymmetric 1,4-addition of zirconium species **III** to α,β-unsaturated ketone **I**. This should, in turn, furnish a rhodium enolate intermediate, whose trapping with aldehyde **II** was expected to lead first to aldol **IV** and thence to enone **V** and disubstituted cyclic ketones **VI** (by sequential elimination of water and reduction, respectively). It was, therefore, hoped that the products from this multicomponent reaction would include any one or more desired compounds **IV** to **VI** (Scheme 2).

This work was initiated with some considerable success, as demonstrated in Scheme 3 in the case of α,β-unsaturated
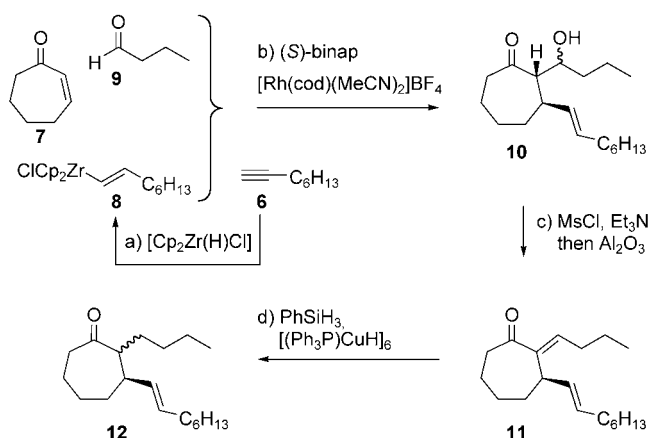
Scheme 3. Proof of principle of the catalytic asymmetric three-component reaction. Reagents and conditions: a) [Cp$_2$Zr(H)Cl], THF, 30 min; b) **7** (1.2 equiv), **8** (1.2 equiv), **9** (1.0 equiv), [Rh(cod)(MeCN)$_2$]BF$_4$ (0.05 equiv), (*S*)-binap (0.06 equiv), THF, 25°C, 12 h, 50% (**10**; ≈4:1 isomeric ratio); c) MsCl (3.0 equiv), Et$_3$N (6.0 equiv), 0→25°C, 30 min; then Al$_2$O$_3$ (excess), 12 h, 95% (**11**, *E:Z*≈20:1, 98% *ee*); d) PhSiH$_3$ (1.5 equiv), [(Ph$_3$P)CuH]$_6$ (1 mol%), toluene, 25°C, 6 h, 85% (*trans/cis*≈1:3). cod = cyclooctadiene, (*S*)-binap = (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Ms = methanesulfonyl.

cycloheptenone (**7**). Thus, mixing of **7** with the zirconium species **8** (derived from 1-octyne and [Cp$_2$Zr(H)Cl])[7] and aldehyde **9** in the presence of [Rh(cod)(MeCN)$_2$]BF$_4$[5] and (*S*)-binap as the catalyst system in THF at 25°C for 12 h led to the formation of **10** as a mixture of two diastereoisomers (≈4:1, 50% combined yield). This mixture was subjected to a standard mesylation/elimination sequence to produce enone **11** (*E/Z*≈20:1; Table 2) in 95% overall yield. Furthermore, and gratifyingly, the enantiopurity of this enone ([α]$_D^{33}$ = +118.5 (CHCl$_3$, c = 1.0)) was found to be 98% *ee* by chiral HPLC (Chiralcel, OD-H). Finally, this enone **11** was reduced with PhSiH$_3$ in the presence of a catalytic amount of [(Ph$_3$P)CuH]$_6$[8] (1 mol%) to afford 2,3-disubstituted cycloheptanones **12** (*trans/cis*≈1:3; 85% combined yield).

With regards to a mechanism for this process, we envisage a similar catalytic cycle (see Scheme 4) to those previously proposed by the Oi and Inoue group[5] and the Hayashi group[6] to explain their enantioselective 1,4-addition of zirconium species, aryl boronic acids, or *B*-aryl-9-BBN
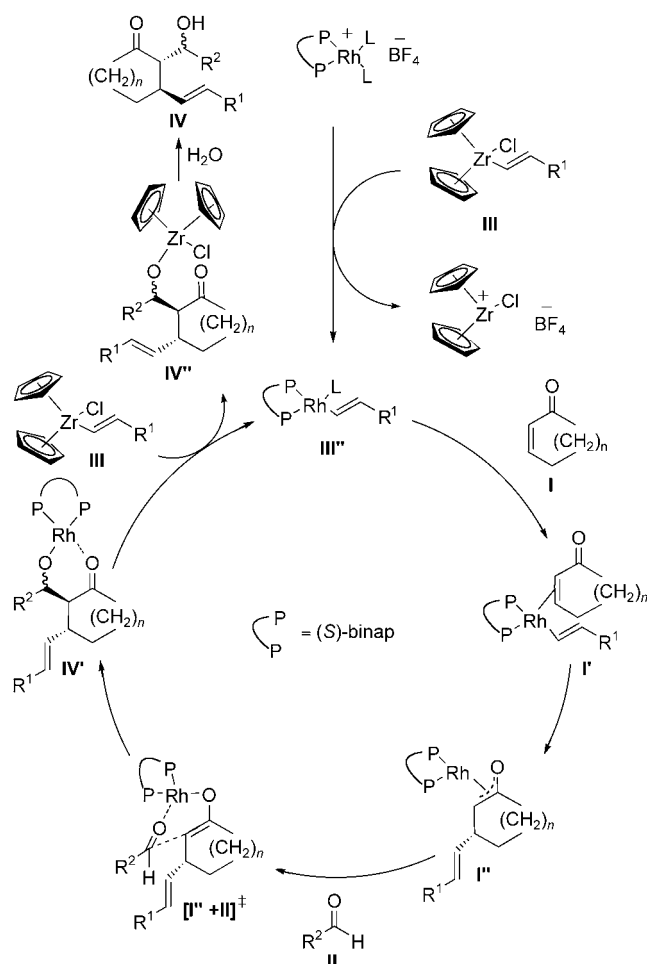
Scheme 4. Proposed mechanism for the asymmetric three-component, rhodium-catalyzed 1,4-addition/aldol reaction (I + II + III→IV). L = CH₃CN, cod (cycloocta-1,5-diene), or thf.

reagents to α,β-unsaturated enones. Thus, transmetalation of the alkenyl zirconium species **III** may lead to the rhodium alkenyl complex **III″**, which could react with cyclic enone **I** to form the π-coordination complex **I′**. Rearrangement of **I′**, upon transfer of the alkenyl group onto the 4-position of the enone, should lead to the rhodium enolate **I″**. This chiral enolate may then engage the aldehyde **II** in an aldol reaction, generating rhodium complex **IV′** through a six-membered-ring transition state [**I″ + II**]‡. Transmetalation of **IV′** with another alkenyl zirconium species **III** could then lead to zirconium alkoxide **IV″** and regeneration of rhodium alkenyl complex **III″**. Hydrolysis of **IV″** provides aldol product **IV**. Both the chemoselectivity of the rhodium alkenyl species **III″** in differentiating between the conjugated ketone **I** and an aldehyde **II**, as well as the ability of the postulated transient rhodium enolate to engage the aldehyde component in an aldol reaction,[9,10] are crucial for the success of this process.

Next, we examined the generality and scope of the present enantioselective reaction. As demonstrated in Table 1, this process proceeded well with five- (Table 1, entries 7 and 8), six- (Table 1, entries 1–6), and seven-membered cyclic enones (Table 1, entries 9–11), as well as an acyclic ketone (Table 1, entry 12). Thus, a series of aldol products **IV** were obtained in

good yields (30–62%) through the three-component 1,4-addition/aldol reaction. Good to excellent enantioselectivities (78–98% ee) were observed for the corresponding enones **V**. Various aliphatic aldehydes that carry linear or branched chains or ring systems at their α sites were employed successfully. It is noteworthy that benzaldehyde and trimethyl acetaldehyde did not prove to be suitable substrates for these reactions. The alkenyl zirconium species employed in these asymmetric processes were derived from terminal alkynes with different aliphatic or functionalized carbon chains.

The developed technology was successfully applied to the synthesis of the spiro system **2** of vannusal A (**1**), as depicted in Scheme 5. Thus, enone **4**, alkenyl zirconium species **8** (generated in situ from 1-octyne and [Cp₂Zr(H)Cl])[7] and aldehyde **13** were combined in the presence of [Rh(cod)(MeCN)₂]BF₄ (5 mol%) and (S)-binap (6 mol%) in THF at
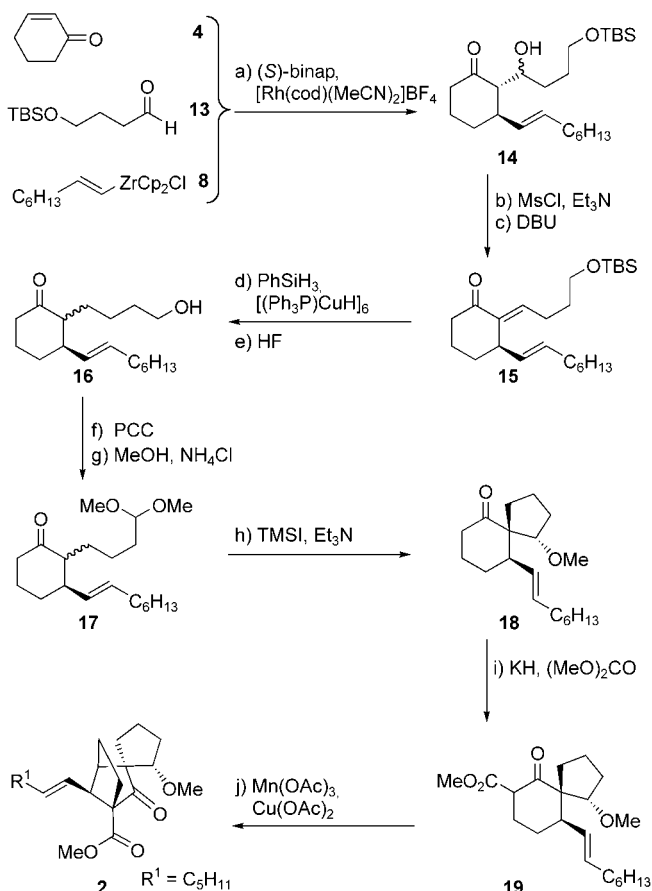
Scheme 5. Construction of spirocyclic building block **2** of vannusal A. Reagents and conditions: a) [Rh(cod)(MeCN)₂]BF₄ (5 mol%), (S)-binap (6 mol%), THF, 25°C, 12 h, 52%; b) MsCl (2.0 equiv), Et₃N (3.0 equiv), CH₂Cl₂, 25°C, 30 min; c) DBU (2.0 equiv), THF, 25°C, 2 h, (**15**, E:Z ≈ 13:1), 85% (over two steps); d) PhSiH₃ (1.5 equiv), [(Ph₃P)CuH]₆ (1 mol%), toluene, 25°C, 6 h, (trans/cis ≈ 2:1); e) aqueous HF (48%;10 equiv), THF, 25°C, 2 h, 79% (over two steps); f) PCC (1.5 equiv), CH₂Cl₂, 25°C, 2 h, 91%; g) MeOH, NH₄Cl (0.01 equiv), reflux, 2 h, 98%; h) TMSI (1.5 equiv), Et₃N (1.2 equiv), CH₂Cl₂, 0 to 25°C, 2 h, 50%; i) KH (5.0 equiv), (MeO)₂CO (10 equiv), THF, reflux, 2 h; j) Mn(OAc)₃ (2.5 equiv), Cu(OAc)₂ (1.2 equiv), EtOH, reflux, 2 h, 68% (over two steps), (**2**, 96% ee). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, PCC = pyridinium chlorochromate, TMS = trimethylsilyl.

Table 1: Catalytic asymmetric three-component 1,4-addition/aldol reaction of enones **I**, aldehydes **II**, and alkenyl zirconium species **III**: preparation of enantiomerically enriched 2,3-disubstituted aldols **IV** and enones **V**.[a]

Entry	I	II	III'	IV	Yield [%][b]	Ratio[c]	V[d]	Yield [%][e]	ee [%][f]	[α]$_D$
1		(propyl aldehyde)	C$_6$H$_{13}$		53	2:1		85	96	+
2		OTBS	C$_6$H$_{13}$		52	1.4:1		85	96	+
3		(cyclohexyl)	C$_6$H$_{13}$		51	4:1		89[g]	96	+
4		(isobutyl)	C$_6$H$_{13}$		41	5.9:1		83[h]	95	+
5			C$_4$H$_9$		30	1.1:1		88	94	+
6			(CH$_2$)$_4$OTBS		58	1:1		80	96	+
7			C$_6$H$_{13}$		55	1:1		91	78	+
8		(cyclohexyl)	C$_6$H$_{13}$		62	5.3:1		94	79	+
9		(cyclohexyl)	C$_6$H$_{13}$		50	1.3:1		80	98	+
10		OTBS	C$_6$H$_{13}$		34	3.1:1		90	93	+
11			(CH$_2$)$_4$OTBS		61	3.7:1		82	94	+
12			C$_6$H$_{13}$		48	mixture[i]		85	85	+

[a] Reactions were carried out at ambient temperature on a 1.0-mmol scale (aldehyde) in THF in the presence of catalytic amounts of [Rh(cod)(MeCN)$_2$]BF$_4$ and (S)-binap (see Experimental Section for more details). [b] Yields of isolated products. [c] Ratios were determined by ^{1}H NMR spectroscopy. The relative configurations were not determined. [d] The E enones were predominantly formed along with small amounts of the Z enones (E/Z > 9:1), unless otherwise specified. The absolute configurations of products in entries 1–11 were tentatively assigned by analogy with their corresponding 1,4-addition products.[5]. [e] Overall yield of mesylation–elimination (**IV**→**V**). [f] The ee values of the E enones were determined by chiral HPLC (chiralpak AD or chiralcel OD-H columns). [g] E/Z ≈ 3:1. [h] E/Z ≈ 5:1. [i] Four isomers by ^{1}H NMR spectroscopy.

25°C. After 12 h of stirring, aldol product **14** was obtained (52% yield, ≈1.4:1 ratio of diastereomers). Mesylation of this mixture, followed by exposure of the resulting products to DBU, furnished enone **15** (E/Z ≈ 13:1; Table 2) in 85% overall yield. The conjugated double bond within **15** was selectively reduced with PhSiH$_3$ in the presence of a catalytic amount of [(Ph$_3$P)CuH]$_6$[8] (1 mol%) which led, after desilylation, to disubstituted cyclohexanones **16** (trans/cis ≈ 2:1, 79% combined yield). From this point, the synthesis followed the sequence established previously on a similar, racemic, substrate.[11] Thus, oxidation of hydroxyketone **16** with PCC, followed by acetalization of the resulting aldehyde, led to **17** (90% yield). Treatment of this acetal **17** with TMSI in the presence of Et$_3$N gave methoxy spiroketone **18** (48% yield of the desired diastereoisomer; Table 2). Finally, carboxymethylation of the latter compound **18**, followed by exposure to the radical oxidation conditions of Mn(OAc)$_3$–Cu(OAc)$_2$, afforded the desired vannusal A key building block **2** (68%;

Table 2). Intermediate **2** ($[\alpha]_D^{33} = -1.0$ (CHCl$_3$, $c = 1.0$)) was thus obtained with 96% *ee*, as determined by chiral HPLC (Chiralcel OD-H).

The methodology presented herein represents a convenient entry into multifunctionalized and relatively complex building blocks, starting from comparatively simple and readily available starting materials. Its scope incorporates substituted acyclic as well as cyclic ketones. Good to excellent enantiomeric excess was attained in all cases studied. Application of this catalytic asymmetric three-component reaction to the construction of the spirocyclic domain of vannusal A powerfully demonstrates the applicability and versatility of this process. The total synthesis of this challenging triterpene **1** is well underway in our laboratories.

Experimental Section

General procedure: The alkyne (1.25 mmol, 1.25 equiv) was added to [Cp$_2$Zr(H)Cl][12] (1.2 mmol; 1.2 equiv) in anhydrous THF (4 mL) under argon. The mixture was stirred at 25°C for 30 min until it became homogeneous. In a separate flask, [Rh(cod)(MeCN)$_2$]BF$_4$ (0.05 mmol, 0.05 equiv) and (*S*)-binap (0.06 mmol, 0.06 equiv) were dissolved in anhydrous THF (4 mL) under argon and stirred at 25°C for 30 min. The enone (1.2 mmol, 1.2 equiv) was then added to the resulting red catalyst solution, followed by the aldehyde (1.0 mmol; 1.0 equiv). The zirconium reagent was transferred to this solution through a cannula, and the resulting mixture was stirred at 25°C for 12 h. The mixture was concentrated under reduced pressure, and the residue taken up in diethyl ether and directly filtered through a small pad of celite and then concentrated. The resultant crude mixture was purified by flash column chromatography (silica gel), with Et$_2$O/hexanes mixtures as eluant, to provide aldol products **IV** as colorless oils. Triethylamine (1.8 mmol, 6.0 equiv) and methanesulfonyl chloride (0.9 mmol, 3.0 equiv) were added to a stirred solution of the aldol product **IV** (0.3 mmol) in CH$_2$Cl$_2$ (4 mL) at 0°C. The resulting mixture was allowed to warm to 25°C within 30 min, and then basic alumina (2 g) was added (alternatively, DBU/THF could be employed for the elimination step). The mixture was then stirred vigorously at 25°C for 12 h, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel) with EtOAc/hexanes mixtures as eluant to provide enone product **V**.

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[2] For an excellent review on asymmetric multicomponent reactions, see: M. Yus, D. J. Ramón, *Angew. Chem.* **2005**, 117, 1602–1634; *Angew. Chem. Int. Ed.* **2005**, 44, 1628–1661.

[3] For examples of catalytic asymmetric 1,4-addition/aldol reactions involving cyclic enones, see: a) K.-I. Yamada, T. Arai, M.

2: $R_f = 0.43$ (silica gel, EtOAc/hexanes 1:5); $[\alpha]_D^{33} = -1.0$ ($c = 1.0$, CHCl$_3$); IR (film): $\tilde{\nu}_{max} = 1731$ cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): $\delta = 5.61$ (dt, $J = 15.0, 7.2$ Hz, 1H), 5.36 (dd, $J = 15.0, 7.2$ Hz, 1H), 3.68 (s, 3H), 3.54 (dd, $J = 6.6, 3.0$ Hz, 1H), 3.26 (s, 3H), 2.85 (d, $J = 7.2$ Hz, 1H), 2.13–1.80 (m, 9H), 1.73 (m, 1H), 1.57 (m, 1H), 1.45 (m, 1H), 1.33–1.17 (m, 7H), 0.86 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): $\delta = 212.1$, 171.4, 136.0, 124.5, 87.6, 69.4, 62.6, 58.3, 53.3, 52.7, 52.1, 36.8, 33.6, 32.1, 32.0, 29.8, 24.4, 23.3, 22.7, 22.4, 14.9 ppm; HRMS (ESI-TOF) (*m/z*): calcd for C$_{21}$H$_{33}$O$_4^+$ [*M*+H]$^+$: 349.2373; found: 349.2357

11: $R_f = 0.46$ (silica gel, EtOAc/hexanes 1:5); $[\alpha]_D^{33} = +118.5$ ($c = 1.0$, CHCl$_3$); IR (film) $\tilde{\nu}_{max} = 2957, 2929, 2855, 1684, 1611, 1458, 1326, 1286, 1208, 1122, 974, 938$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 6.52$ (t, $J = 7.6$ Hz, 1H), 5.51 (dd, $J = 15.7, 4.0$ Hz, 1H), 5.30 (m, 1H), 3.60 (m, 1H), 2.59 (dt, $J = 13.5, 2.0$ Hz, 1H), 2.46 (m, 1H), 2.11–1.97 (m, 5H), 1.88–1.79 (m, 1H), 1.78–1.70 (m, 2H), 1.59–1.50 (m, 1H), 1.49–1.20 (m, 11H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.87 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 216.2$, 143.0, 140.0, 131.6, 130.7, 43.4, 37.8, 34.2, 32.7, 31.7, 30.0, 29.4, 28.8, 25.8, 25.1, 22.6, 22.1, 14.1, 14.0 ppm; HRMS (ESI TOF) (*m/z*): calcd for C$_{19}$H$_{33}$O$^+$ [*M*+H]$^+$: 277.2526; found: 277.2531

15: $R_f = 0.41$ (silica gel, EtOAc/hexanes 1:5); $[\alpha]_D^{33} = +73.5$ ($c = 1.0$, CHCl$_3$); IR (film) $\tilde{\nu}_{max} = 2928, 2856, 1688, 1616, 1471, 1463, 1256, 1102, 970, 837, 776$ cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 6.64$ (t, $J = 7.5$ Hz, 1H), 5.34 (dd, $J = 15.4, 4.8$ Hz, 1H), 5.23 (m, 1H), 3.60 (m, 3H), 2.48 (d, $J = 17.6$ Hz, 1H), 2.23 (m, 2H), 2.08 (m, 1H), 1.96 (m, 2H), 1.91–1.78 (m, 3H), 1.78–1.71 (m, 1H), 1.68–1.56 (m, 2H), 1.32–1.20 (m, 8H), 0.88 (m, 12H), 0.03 ppm (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 201.8$, 140.2, 138.5, 131.9, 131.3, 62.4, 40.2, 38.6, 32.5, 31.7, 31.6, 29.8, 29.4, 28.8, 25.9, 24.1, 22.6, 19.0, 14.0, −5.3 ppm; HRMS (ESI-TOF) (*m/z*): calcd for C$_{24}$H$_{45}$O$_2$Si$^+$ [*M*+H]$^+$: 393.3183; found: 393.3184

18: $R_f = 0.38$ (silica gel, EtOAc/hexanes 1:10); $[\alpha]_D^{33} = +44.6$ ($c = 1.0$, CHCl$_3$); IR (film): $\tilde{\nu} = 1710$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 5.37$ (dt, $J = 14.8, 6.8$ Hz, 1H), 5.21 (ddt, $J = 14.8, 9.6, 1.2$ Hz, 1H), 3.92 (dd, $J = 4.8, 2.4$ Hz, 1H), 3.21 (s, 3H), 2.49 (m, 1H), 2.38–2.30 (m, 2H), 2.25–2.10 (m, 2H), 1.96–1.56 (m, 8H), 1.45 (m, 1H), 1.37–1.18 (m, 9H), 0.85 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): $\delta = 212.8$, 133.9, 129.7, 88.3, 65.3, 57.4, 48.7, 42.1, 33.3, 32.5, 30.2, 30.0, 29.9, 29.6, 29.6, 23.6, 23.5, 21.6, 14.9 ppm; HRMS (ESI-TOF) (*m/z*): calcd for C$_{19}$H$_{33}$O$_2^+$ [*M*+H]$^+$: 293.2471; found: 293.2475

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