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Organocatalytic asymmetric multi-component [C+NC+CC] synthesis of highly functionalized pyrrolidine derivatives

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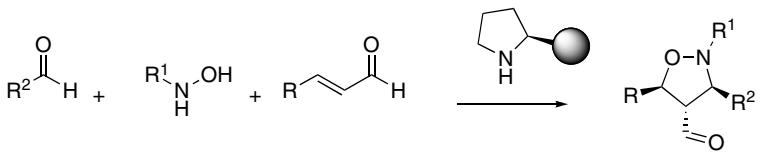
Abstract—The highly chemo- and enantioselective organocatalytic [C+NC+CC] coupling process between aldehydes, dialkyl 2-aminomalonates and α,β-unsaturated aldehydes is presented. The reaction gives access to highly functionalized pyrrolidine derivatives in good yields with >10:1 dr and 90–98% ee.

The pyrrolidine ring is an important structural motif found in several bioactive molecules. For example, it is present in the neuroprotective agent kaitocephalin,[1] the influenza drug A-192558,[2] and the antitumor antibiotic bioxalomycin β1.[3] Pyrrolidines also serve as useful molecular scaffolds for the exploration and exploitation of pharmacophore space via diversity-oriented synthesis (DOS),[4–6] which has led to the findings of new drug leads for the treatment of cancer[7] and hepatitis C viral infections.[8] Thus, intense research is ongoing for the development of new stereocontrolled routes to chiral pyrrolidines. For example, asymmetric methods that rely on 1,3-dipolar cycloaddition reactions have been developed for their preparation.[9,10] In this area, organometallic complex-catalyzed enantioselective cycloaddition transformations between azomethine ylides and electron-deficient alkenes (normal electron demand reaction) have been successfully employed for the synthesis of functional pyrrolidines.[4,11] In the rapidly growing research field of organocatalysis, MacMillan first reported a catalytic enantioselective synthesis of isoxazolidines based on the chiral imidazolidinone catalyzed 1,3-dipolar cycloaddition between preformed nitrones and enals.[12–18] The iminium activation mechanism, which is central in this type of catalysis, has been successfully applied in several asymmetric reactions. In this context, we recently reported a catalytic, highly enantioselective isoxazolidine synthesis based on an organocatalytic asymmetric multi-component 1,3-dipolar cycloaddition (Eq. 1).[19]



(1)

Recently, Garner et al. reported a stereoselective synthesis of functional pyrrolidines based on the union of an aldehyde ('C'), an amino acid derivative ('NC'), and an electron-deficient alkene ('CC') using a chiral auxiliary in what they termed a three-component

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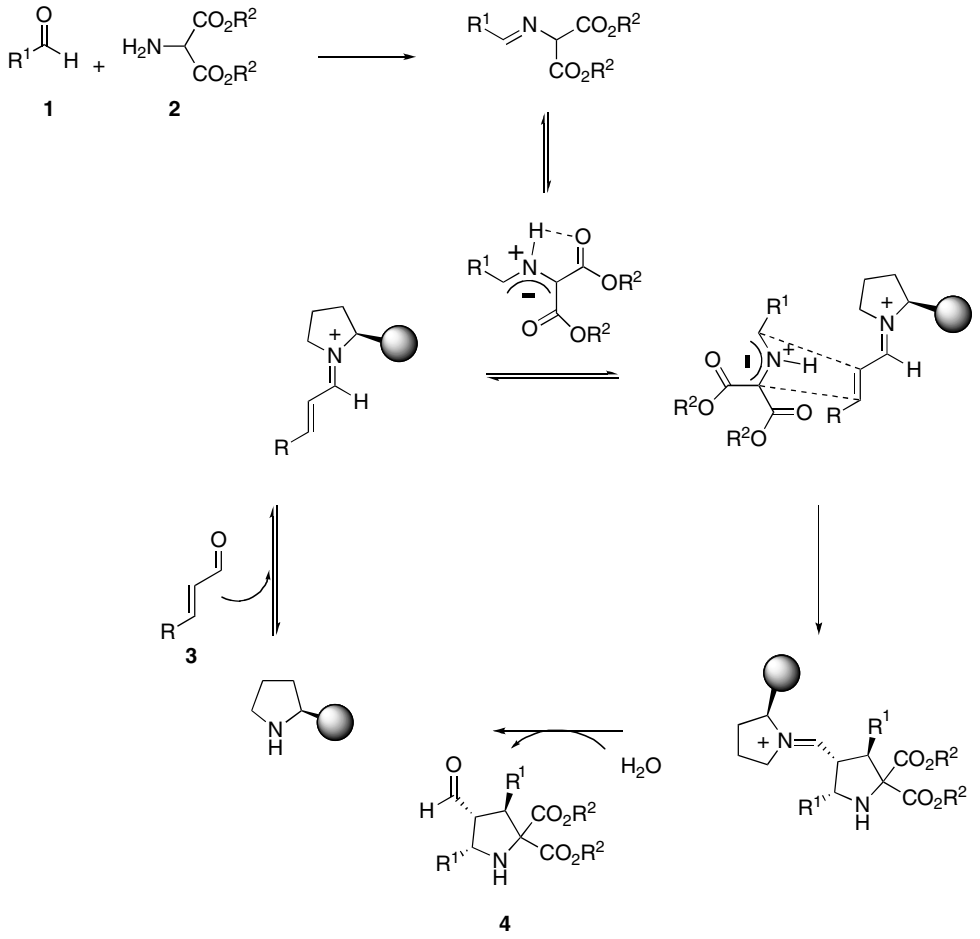


Scheme 1. Organocatalytic asymmetric aldehyde → imine → dipole → cycloadduct reaction cascade.

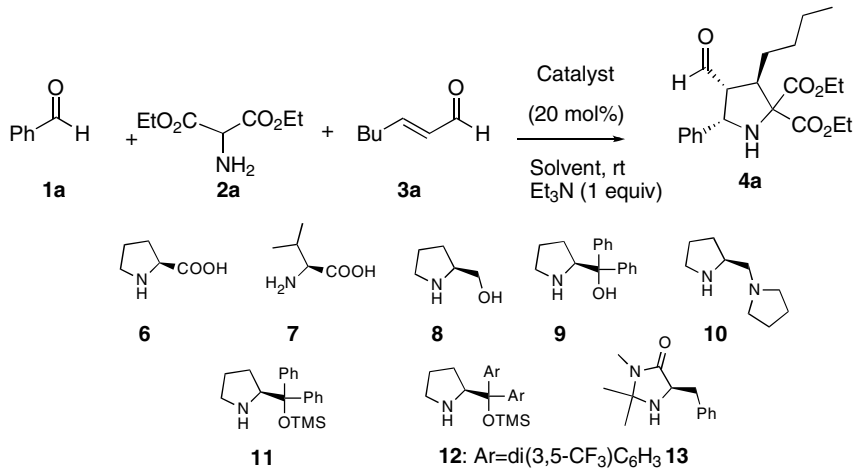
[C+NC+CC] coupling reaction.[20] Notably, Schreiber reported one example of a one-pot, three-component synthesis of a highly substituted pyrrolidine derivative catalyzed by a chiral silver complex.[4] Inspired by these findings and the importance of asymmetric multi-component reactions,[4,19–21] we envisioned that a small chiral amine would be able to catalyze an asymmetric three-component cascade imine → azomethine ylide → 1,3-dipolar cycloaddition [C+NC+CC] sequence according to Scheme 1. To the best of our knowledge, no report of an organocatalytic highly enantioselective pyrrolidine synthesis based on an asymmetric multi-component 1,3-dipolar cycloaddition has been disclosed to date.[22]

Herein, we present a highly chemo- and enantioselective one-pot, three-component organocatalytic route to the synthesis of valuable pyrrolidine derivatives in good yields with 3:1–>10:1 dr and 90–98% ee.

In an initial catalyst screen for the reaction between benzaldehyde **1a** (0.375 mmol), diethyl 2-aminomalonate **2a** (0.375 mmol), and 2-heptenal **3a** (0.25 mmol), we found that proline **6** and primary amino acids such as valine **7** catalyzed the chemoselective formation of functionalized pyrrolidine **4a** in high conversion and moderate enantioselectivity (Table 1). Simple chiral pyrrolidines such as **8**–**12** also catalyzed the asymmetric formation of **4a**. In addition, MacMillan's amino acid derivative **13** catalyzed the formation of **4a** in low conversion and with excellent diastereoselectivity (19:1 *endo*/*exo*) but low enantioselectivity under our reaction conditions (entry 8). To our delight, the protected diarylprolinol **11**[23] catalyzed the formation of **4a** with high efficiency and excellent enantioselectivity in $CHCl_3$ (entry 6).[24] The chiral pyrrolidine **4a** was the only product observed by proton NMR analyses of the crude reaction mixture, however, the chiral pyrrolidine **4a** is rather unstable and decomposed upon isolation and storage. The highest diastereo- and enantioselectivity for the reaction was achieved when $CHCl_3$ or toluene was used as the solvent. For example, the highest dr (*endo*/*exo*) was accomplished in toluene when the aliphatic enal **3a** was used as the substrate (entry 9). Moreover, the addition of a stoichiometric amount of triethylamine (TEA) improved the diastereoselectivity of the reaction.

Thus, we decided to investigate the scope of the catalytic asymmetric one-pot, three-component reaction using toluene and $CHCl_3$ as the solvent, TEA as an additive and chiral amine **11** as the catalyst (Table 2).

Table 1. Catalyst screen for the one-pot reaction between **1a**, **2a**, and **3a**



Entry	Catalyst	Solvent	Time (h)	Conv.[a] (%)	dr[b]	ee[c] (%)
1	**6**	$CHCl_3$	20	100	8:1	50
2	**7**	$CHCl_3$	66	66	2:1	17
3	**8**	$CHCl_3$	20	76	5:1	33
4	**9**	$CHCl_3$	20	<10	n.d.	n.d.
5	**10**	$CHCl_3$	20	90	2:1	33
6	**11**	$CHCl_3$	44	100	3:1	97
7	**12**	$CHCl_3$	20	52	3:2	39
8	**13**	$CHCl_3$	20	19	19:1	13
9	**11**	Toluene	20	100 (51)[d]	10:1 (10:1)[d]	95 (95)[d]
10	**11**	DMF	20	52	3:2	29
11	**11**	CH_3CN	20	70	3:2	26

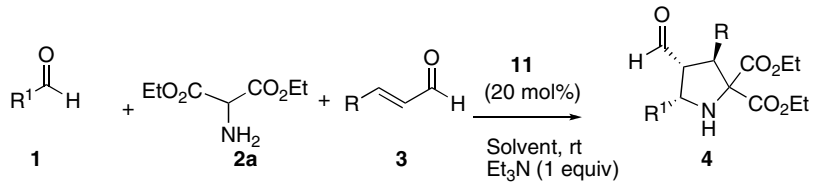
[a] Conversion of **3a** as determined by NMR analyses of the crude reaction mixture.
[b] *endo*/*exo*-Ratio determined by NMR analyses of the crude reaction mixture.
[c] Determined by chiral-phase HPLC analyses of **4a**.
[d] The results for the isolated product after silica-gel column chromatography.

The organocatalytic enantioselective three-component reactions were highly chemo- and enantioselective. The corresponding chiral pyrrolidine derivatives **4** were obtained in 50–63% yields with 3:1–>10:1 dr and 90–98% ee. For example, the reaction between benzaldehyde **1a**, 2-aminomalonate **2a**, and cinnamic aldehyde **3b** gave the corresponding product **4d** in 63% yield with 10:1 dr and 95% ee (entry 4). Several different aromatic and aliphatic enals **3** could be used as acceptors for the reaction. Moreover, various benzaldehyde derivatives were used as the aldehyde moiety. The reactions were also readily performed in parallel. Thus, the one-pot, three-component organocatalytic cascade [C+NC+CC] coupling process should be useful as a platform in diversity-oriented synthesis (DOS) of pyrrolidine derivatives with three contiguous chiral centers. The chiral pyrrolidine catalyzed asymmetric cascade [C+NC+CC] reaction could also be extended to a one-pot in situ oxidation to obtain the more stable acid functionalized chiral pyrrolidine derivative **14** (Scheme 2).[25] For example, the one-pot organocatalytic asymmetric tandem 1,3-reaction dipolar/oxidation sequence between aldehyde **1a**, aminomalonate **2a**, and enal **3b** gave the corresponding acid **14d** in 52% yield with 10:1 dr and 95% ee. Next, pure acid **14d** was converted quantitatively to the corresponding chiral proline derivative **15d** (1:1 mixture of two diastereoisomers) under acidic conditions.[26] Quantitative methylation of diacid **15d** gave proline derivatives **16d**[27] and **16d′** as single diastereomers after isolation. Thus, the chiral pyrrolidine catalyzed one-pot reaction can be used as a novel route for the preparation of useful chiral proline derivatives with four contiguous stereocenters.

Comparison with the literature revealed the relative configuration of **16d** and established the stereochemistry of pyrrolidine derivatives **4**.[27] This is in accordance with previous chiral pyrrolidine **11** catalyzed 1,3-dipolar cycloadditions.[12d,19] Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of **11** leads to stereoselective *Re*-facial *endo*-addition to the activated olefin via the plausible transition state depicted in Scheme 1.

In summary, we have described a simple highly chemo- and enantioselective organocatalytic one-pot, three-component, cascade [C+NC+CC] reaction sequence between aldehydes, dialkyl aminomalonate, and α,β-unsaturated aldehydes. The reaction represents a versatile asymmetric entry to a variety of valuable highly functionalized pyrrolidine derivatives in good yields with 3:1–>10:1 dr and 90–98% ee. Mechanistic studies, synthetic applications of this transformation in DOS as well as the development of other enantioselective multi-component reactions are ongoing in our laboratory.

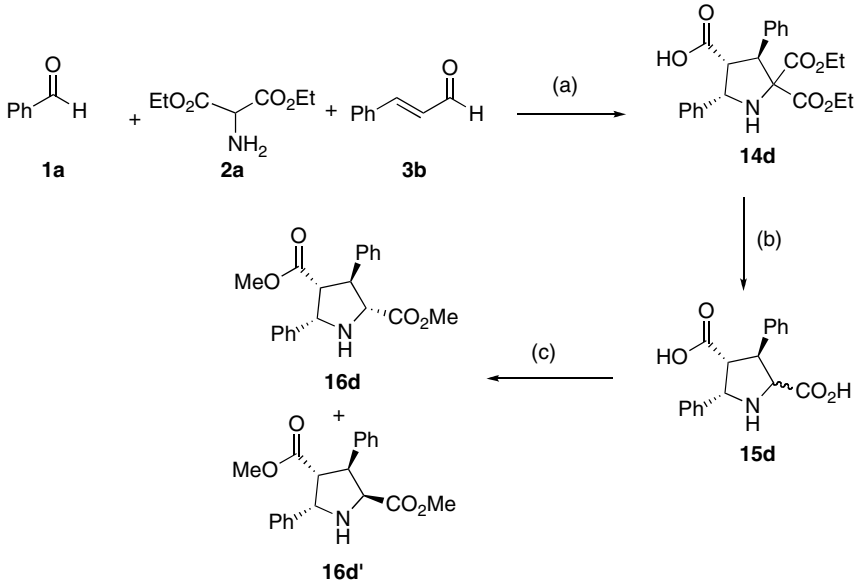
Table 2. Scope of the organocatalytic three-component reaction



1 2a 3 4

Entry	R	R^1	Product	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	*n*-Bu	Ph	**4a**	20	51[d]	10:1	95
2	*n*-Bu	4-BrC_6H_4	**4b**	20	58[d]	8:1	92
3	*n*-Bu	4-$NO_2C_6H_4$	**4c**	20	59[d]	5:1	93
4	Ph	Ph	**4d**	20	63[e]	10:1	95
5	*n*-Bu	4-$MeOC_6H_4$	**4e**	20	61[e]	3:1	98
6	Ph	Ph	**4f**	20	58[d]	>10:1	90
7	4-BrC_6H_4	Ph	**4g**	20	60[e]	10:1	92
8	4-ClC_6H_4	Ph	**4h**	20	52[e]	8:1	97
9	2-Naphth	Ph	**4i**	20	60[e]	8:1	96
10	*n*-Pr	4-BrC_6H_4	**4j**	44	57[e]	5:1	98
11	4-ClC_6H_4	4-ClC_6H_4	**4k**	44	50[e]	8:1	97
12	Ph	4-CNC_6H_4	**4l**	44	52[e]	6:1	92
13	*n*-Pr	4-ClC_6H_4	**4m**	44	58[e]	6:1	96
14	*n*-Hex	4-CNC_6H_4	**4n**	44	55[e]	5:1	95
15	*n*-Et	4-ClC_6H_4	**4o**	20	55[e]	5:1	92
16	*n*-Pr	4-MeC_6H_4	**4p**	20	62[e]	4:1	98

[a] Isolated yield of the pure product **4** after silica-gel chromatography.
[b] *endo*/*exo*-Ratio determined by NMR analyses of the crude reaction mixture.
[c] Determined by chiral-phase HPLC analyses.
[d] Reaction run in toluene.
[e] Reaction run in $CHCl_3$.



1a 2a 3b 14d 15d 16d 16d'

Scheme 2. Reagents and conditions: (a) (i) (*S*)-**11** (20 mol %), Et_3N, $CHCl_3$, rt, 20 h, 85%; (ii) $NaClO_2$, isobutene, $KHPO_4$, *t*-BuOH–H_2O 2:1, 52%. (b) HCl (6 N), AcOH, reflux, 16 h, >99%. (c) $TMSCHN_2$, benzene–MeOH, rt, 1.5 h, >99%.

Acknowledgments

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appeared on the web on 30th May describing an organocatalytic reaction between a preformed azomethine ylide derived from diethyl 2-aminomalonate and enals. Notably, catalyst **11** did not catalyze the reaction under their reaction conditions.

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24. *Typical experimental procedure for the organocatalytic three-component synthesis of chiral pyrrolidines*. To a stirred solution of aldehyde **1** (0.375 mmol, 1.5 equiv) in $CHCl_3$ or toluene, diethyl aminomalonate **2** (0.375 mmol, 1.5 equiv) was added. The reaction was stirred at room temperature for 1 h and then catalyst **11** (0.05 mmol, 20 mol %), TEA (0.25 mmol, 1.0 equiv), and α,β-unsaturated aldehyde **3** (0.25 mmol, 1.0 equiv) were added. The reaction was then stirred at room temperature for the time shown in Table 2. Next, the crude was purified by silica-gel column chromatography to afford the pyrrolidine derivative **4**. Compound **4a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.03$ (d, $J = 4.4$ Hz, 1H), 7.35–7.20 (m, 5H), 5.13 (d, $J = 9.2$ Hz, 1H), 4.37–4.21 (m, 4H), 3.32–3.25 (m, 1H), 3.07–3.00 (br s, 1H), 2.95–2.87 (m, 1H), 1.80–1.70 (m, 2H), 1.36–1.20 (m, 10 H), 0.92–0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 202.2, 171.8, 169.6, 138.9, 128.6, 127.7, 127.1, 75.1, 61.9, 61.7, 61.7, 59.6, 44.0, 30.4, 30.2, 22.7, 14.2, 14.0, 13.8. $[\alpha]_D^{23}$ −33.5 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+H]^+$ ($C_{21}H_{30}NO_5$) requires *m*/*z* 376.2118, found 376.2108. The enantiomeric excess was determined by HPLC with an AD column. (*n*-hexane–*i*-PrOH = 98:2, $\lambda = 250$ nm), 1.0 mL/min; t_R = major enantiomer 15.7 min, minor enantiomer 10.7 min.
25. *Typical experimental procedure for the one-pot organocatalytic three-component synthesis of acid functionalized pyrrolidine* **14d**: To a stirred solution of aldehyde **1a** (0.375 mmol) in $CHCl_3$, diethyl aminomalonate **2a** (0.375 mmol) was added. The reaction was stirred at room temperature for 1 h and then catalyst **11** (0.05 mmol, 20 mol %), TEA (0.25 mmol, 1.0 equiv), and cinnamic aldehyde **3b** (0.25 mmol) were added. After stirring for 20 h at room temperature, the reaction temperature was decreased to 0 °C and then isobutene (0.1 mL), *tert*-butanol (0.4 mL), H_2O (0.2 mL), KH_2PO_4 (54.4 mg, 4 mmol), and $NaClO_2$ (36 mg, 4 mmol) were added sequentially. The reaction was allowed to reach room temperature. After vigorous stirring overnight, the crude was purified by column chromatography on silica-gel (pentane/EtOAc mixtures) to afford the desired acid **14d**. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.05 (m, 10H), 5.21 (d, $J = 9.2$Hz, 1H), 4.65 (d, $J = 11.2$ Hz, 1H), 4.32–4.20 (m, 2H), 3.94–3.85 (m, 2H), 3.58–3.49 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.77 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 171.7, 169.4, 140.4, 136.5, 128.5, 128.2, 128.1, 127.7, 127.5, 127.2, 76.5, 62.4, 61.8, 58.8, 49.8, 14.0, 13.3. $[\alpha]_D^{23}$ +28.3 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+H]^+$ ($C_{23}H_{26}NO_6$) requires *m*/*z* 412.1755, found 412.1740.
26. *Experimental procedure for the synthesis of highly functionalized proline derivatives*: Compound **14d** (0.073 mmol) was dissolved in AcOH (0.15 mL) and HCl (6 N, 0.6 mL). The reaction was stirred at reflux for 16 h. Next, the crude mixture was diluted with water and washed with EtOAc. The aqueous layer was dried under reduced pressure to afford the proline derivative **15d** in a 1:1 diastereomeric mixture in quantitative yield. Compound **15d** (1:1 mixture of diastereoisomers): colorless solid. Mp 214–216 °C. ^{1}H NMR (400 MHz, D_2O): $\delta = 7.60$–7.20 (m, 10H), 5.60–5.50 (m, 1H), 5.48–5.40 (m, 1H), 5.10–5.02 (m, 1H), 4.75–4.65 (m, 1H), 4.65–4.55 (m, 1H), 4.30–4.20 (m, 1H), 4.05–3.95 (m, 1H), 3.90–3.80 (m, 1H). HRMS (ESI): calcd for $[M+H]^+$ ($C_{18}H_{18}NO_4$) requires *m*/*z* 312.1230, found 312.1239.
27. To a 5 mL round bottom flask containing compound **15d** (0.1 mmol) in benzene (1 mL) was added MeOH (0.2 mL) and the reaction mixture was stirred for 5 min. Next, $TMSCHN_2$ (0.150 mL) was added dropwise. The reaction mixture was stirred for 90 min followed by the removal of the solvent under reduced pressure. The crude mixture was purified by silica-gel column chromatography (pentane/EtOAc mixtures) to afford the pure diastereomers. Compound **16d**: colorless solid. Mp 64–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$–7.22 (m, 10H), 4.87 (d, $J = 8.8$ Hz, 1H), 4.09 (d, $J = 8.8$ Hz, 1H), 3.90 (t, $J = 8.4$ Hz, 1H), 3.72 (s, 3H), 3.54 (t, $J = 8.4$ Hz, 1H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.1, 172.0, 140.2, 139.3, 129.0, 128.5, 128.0, 127.8, 127.4, 127.2, 67.8, 65.5, 59.0, 52.5, 52.4, 51.5. $[\alpha]_D^{23}$ +19.2 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+Na]^+$ ($C_{20}H_{21}NO_4Na$) requires *m*/*z* 362.1363, found 362.1372. The data matched those for previously reported **16d** see: Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.