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The organocatalytic direct self-trimerization of acrolein: application to the total synthesis of montiporyne F

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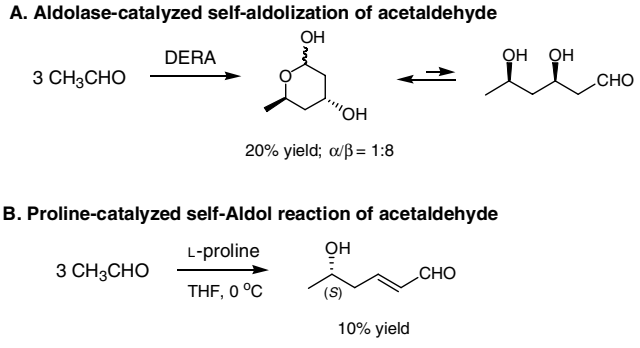
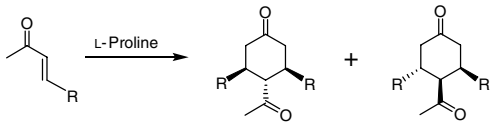
Abstract—The organocatalytic direct self-trimerization of acrolein, via cascade double-Michael and Mannich reactions, affording 5-methylenecyclohex-3-ene-1,3-dicarbaldehyde (**1**) is described. Synthetic application of the reaction was demonstrated by further transformations of **1** to montiporyne F.

Natural compounds occurring as dimers or trimers of monomers are common in nature;[1] applications of the concepts of catalytic dimerization and trimerization have led to remarkable advances in the total synthesis of complex molecules.[2] Recently, the discovery and application of enzymes[3] and enzyme-mimetic catalysts,[4] (e.g., organocatalysts)[5] in organic synthesis has received a great deal of attention. For example, Wong and co-workers reported that 2-deoxyribose-5-phosphate aldolase (DERA) catalyzed the double-aldol sequence of acetaldehyde, affording tetrahydro-6-methyl-2*H*-pyran-2,4-diol, (Scheme 1, Type A).[6] Recently, Barbas and co-workers developed the direct asymmetric self-aldolization of 3 equiv of acetaldehyde (i.e., a trimer of acetaldehyde) via cascade aldol and Mannich reactions, affording (+)-(5*S*)-hydroxy-(2*E*)-hexenal in 2–13% yield (Scheme 1, Type B).[7] These two interesting one-pot multi-step transformations have illuminated a new route to efficient synthesis catalyzed by enzyme and enzyme-like compounds. However, the low yields of these reactions remained a serious drawback. More recently, Barbas and co-workers reported the L-proline- or pyrrolidine-catalyzed self-cycloaddition of α,β-unsaturated ketones, providing cyclohexanone derivatives in a higher yield and with a subtle enantioselectivity (Scheme 2).[8] In relation to the elegance of these reactions, the exploration of novel organocatalytic cycloaddition remains a formidable challenge. Herein, we report an unprecedented, novel organocatalytic trimerization of acrolein and its application to the synthesis of a marine natural product.



Scheme 1. Trimerization of acetaldehyde.

During the course of searching for new cycloadditions,[9] we isolated an intriguing dialdehyde products **1** in a 27% yield when freshly distilled acrolein[10] was treated with L-proline in DMF at an ambient temperature for 14 h (Scheme 3). The novel adduct may be produced through the stepwise cascade double-Michael/Mannich reaction



Scheme 2. Proline-catalyzed self Diels–Alder reactions of α,β-unsaturated ketones.

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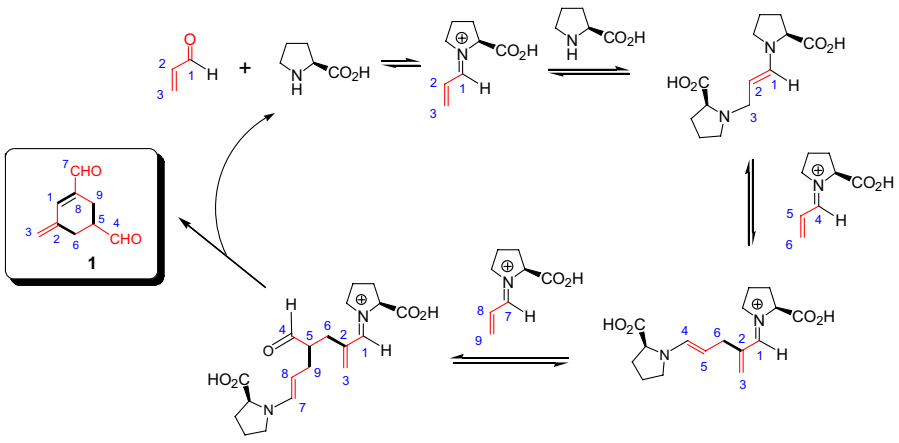
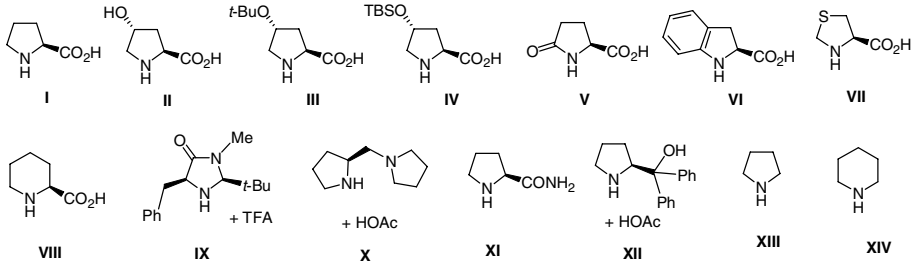


Scheme 3. Proposed reaction mechanism for the proline-catalyzed trimerization of acrolein.

and equilibrium process shown in Scheme 3.[11] It is likely that the product of the proline-catalyzed double-Michael reaction of acrolein subsequently adds to another acrolein molecule via the Mannich reaction to yield the cyclohexenedial product. To the best of our knowledge, this process is the first example of a cascade double-Michael/Mannich reaction of an α,β-unsaturated aldehyde.[12] The structure of **1** was assigned unambiguously by its COSY, HMBC, HMQC, and INADEQUATE spectra and analysis.[13] Unfortunately, dialdehyde **1** obtained was found to be a racemate, by chiral GC–MS analysis.[14] In order to increase the reaction yield, the reaction was performed in the presence of various organocatalysts and conditions. Selected results are summarized in Table 1.

Generally, the reactions proceeded smoothly when monitored by TLC. Except for the polymerization residue, dialdehyde **1** is the major product shown above the baseline residue on TLC and is the only isolable product.

Table 1. Catalyst screening and optimization for the direct catalytic trimerization of acrolein



Entry	Catalyst[e]	Additive	T (°C)	Solvent	Time[b] (h)	Yield[a] (%)
1	**I**		25	DMF	14	27
2	**I**		25	DMSO	14	**40**
3	**I**		25	CH_2Cl_2	14	20
4	**I**		25	THF	14	~0[c]
5	**I**		25	EtOH	14	8
6	**I**		25	CH_3CN	14	**55**
7	**I**[f]		25	CH_3CN	12	40
8	**I**	Imidazole	25	CH_3CN	14	15
9	**I**	Pyrrolidine	25	CH_3CN	24	8
10	**I**	Piperidine	25	CH_3CN	24	8
11	**I**	Spartein	25	CH_3CN	3	58
12	**I**	Spartein	0	CH_3CN	30	26
13	**I**	Et_3N	25	CH_3CN	3	**61**
14	**I**	Et_3N	0	CH_3CN	36	20
15	**II**		25	CH_3CN	24	~0[c]
16	**III**		25	CH_3CN	5	**52**
17	**IV**		25	CH_3CN	10	**48**
18	**V**		25	CH_3CN	24	~0[c]
19	**VI**		25	CH_3CN	24	~0[c]
20	**VII**		25	CH_3CN	24	~0[c]
21	**VIII**		25	CH_3CN	24	~0[c]

Table 1 (*continued*)

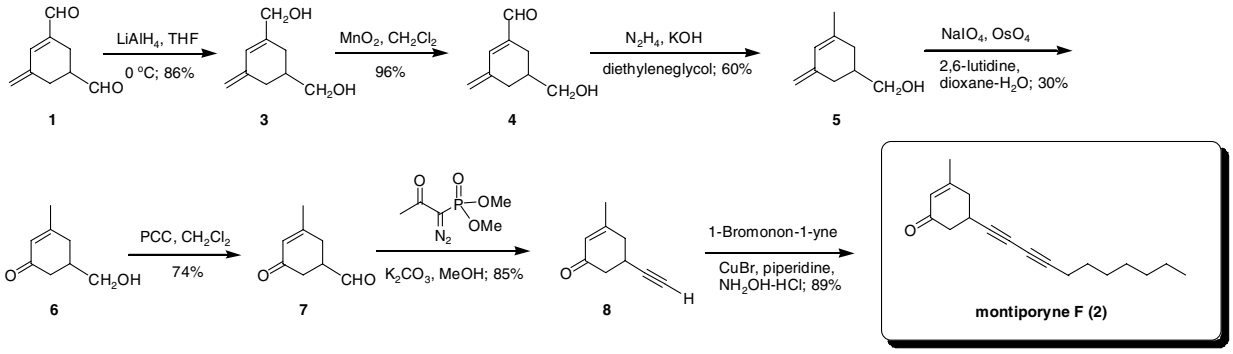
Entry	Catalyst[e]	Additive	*T* (°C)	Solvent	Time[b] (h)	Yield[a] (%)
22	**IX**		25	CH_3CN	24	~0[c]
23	**X**		25	CH_3CN	3	**56**
24	**XI**		25	CH_3CN	24	~0[c]
25	**XII**		25	CH_3CN	14	~0[c]
26	**III**	Spartein	0	CH_3CN	30	34
27	**IV**	Spartein	0	CH_3CN	30	31
28	**X**	Spartein	0	CH_3CN	30	25
29	**XIII**		25	CH_3CN	18	~0[c]
30	None	HOAc	25	CH_3CN	24	~0
31	**XIII**	HOAc	25	CH_3CN	18	5
32	**XIII**	HOAc	25	CH_3CN	**1**[d]	30
33	**XIII**	TFA	25	CH_3CN	24	25
34	**XIII**	TsOH	25	CH_3CN	24	5
35	**XIII**	HFIP	25	CH_3CN	36	5
36	**XIII**	Oxalic acid	25	CH_3CN	6	23
37	**XIV**	HOAc	25	CH_3CN	6	25

[a] Isolated yield.
[b] Reactions were allowed to proceed until acrolein was consumed.
[c] Polymerization.
[d] Reaction completed in 1 h with much of polymerization residue.
[e] Unless otherwise noted, 0.33 equiv of the catalyst was used.
[f] 1.0 equiv of the catalyst was used.

The polar polymerization residue can be easily separated on TLC and removed by flash column chromatography.

The reactions in different solvents were screened, and the highest yield of 55% was observed in CH_3CN (Table 1, entries 1–6). The reaction with a large amount of proline afforded no improvement, but reduced the yield (Table 1, entry 7). Recently, co-catalyst effects on chemoselectivity and stereoselectivity have been reported.[15] Several such additives were applied in the reactions for this study. The addition of Et_3N and spartein accelerated the reaction and increased its yield (Table 1, entries 8–14). Attempts to improve the yield and stereoselectivity by perfoming the reaction at a low temperature (0 °C) resulted in a reduced yield with no enantioselectivity, (Table 1, entries 12 and 14). A series of organocatalysts was screened for the cascade reaction, (Table 1, entries 15–25).[16] Among them, catalysts **III**, **IV**, and **X** are the most promising candidates for the transformation at ambient temperature. Unfortunately, reaction with these catalysts at 0 °C gave lower yields, even with the addition of spartein (Table 1, entries 26–28). Since these chiral amines provided racemate **1**, we studied simple pyrrolidine and piperidine as achiral amine catalysts of this reaction.[17] The reaction gave dialdehyde **1** when an equal amount of acetic acid and base was used as an additive (Table 1, entries 29–37). These results imply that the suitable bifunctional amine–acid catalysts,[18] with the Brønsted acid[19] and Lewis base functionalities cooperating in the catalysis, is required to promote the reaction.

The Michael-type reaction[20] and Mannich reaction[21] are involved in many biosynthetic pathways.[22] As far as we are aware, our current organocatalyzed tandem double-Michael/Mannich reaction has not been reported previously under conventional conditions. Since acrolein[23] and the 1,3,5-trialkyl benzenes[24] have been isolated from many natural sources, it is interesting to speculate about whether this type of cascade reaction is a biotransformation process and can be observed in nature. We envisioned dialdehyde **1** would be a versatile synthon for other synthetically valuable building blocks.[25] To demonstrate the synthetic potential of this reaction, dialdehyde **1** was transferred to montiporyne F (**2**), a natural product isolated from the stony coral *Montipora* sp. having some cytotoxic activities against human solid



Scheme 4. Total synthesis of montiporyne F.

tumor cell lines (Scheme 4).[26] The reduction of **1** to **3** ($LiAlH_4$, THF, 0 °C; 86%) followed by the selective oxidation of the allylic alcohol (MnO_2, CH_2Cl_2; 96%) afforded **4.** Wolff–Kishner reduction of **4** (N_2H_4, KOH, $(HOCH_2CH_2)_2O$; 60%), followed by a modified oxidative cleavage of the methylene group by Lemieux–Johnson reagent with an improved procedure[27] ($NaIO_4$, OsO_4, 2,6-lutidine, dioxane–H_2O; 30%) provided hydroxyenone **6**, which was oxidized (PCC, CH_2Cl_2; 74%) to give ketoaldehyde **7**. Modified Seyferth–Gilbert homologation[28] of ketoaldehyde **7** by the Ohira–Bestmann procedure[29] afforded ketoalkyne **8** in an 85% yield. Cadiot-Chodkiewicz coupling of **8** with 1-bromonon-1-yne (CuBr, piperidine, $NH_2OH{\cdot}HCl$; MeOH) gave montiporyne F (**2**) in an 89% yield.[30]

In summary, the organocatalytic direct asymmetric self-trimerization of acrolein affording dialdehyde **1** on a multigram scale has been developed.[31] Our study further demonstrates that the organocatalyst (e.g., proline and bifunctional amine–acid catalysts) not only acts as the catalyst for organic reactions but can also affect reactions by giving rise to products that do not form with conventional reagents. The facile reaction provides a useful and unique building block for organic synthesis that has been implemented in the total synthesis of montiporyne F. Further investigations of this reaction with respect to its detailed mechanism, as well as more applications of **1** in other total synthesis are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.055.

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31. Reaction of crotonaldehyde and proline led to the formation of [3+3] cycloaddition adducts, see Ref. 9a.