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Rapid Assembly of Polycyclic Substances by a Multicomponent Cascade (4 + 2)−(2 + 2) Cycloadditions: Total Synthesis of the Proposed Structure of Paesslerin A

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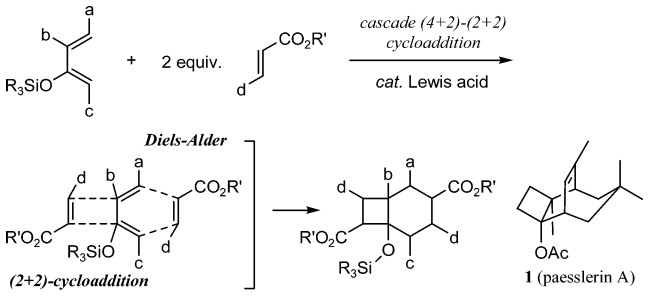
A large variety of organic substances having complicated polycyclic structures and a wide assortment of stereogenic centers are found in nature. These compounds often exhibit attractive and specific biological activities. From the synthetic chemists' point of view, ideal strategies for preparing these structurally complex substances would involve sequences in which stereocontrolled formation of multiple carbon−carbon bonds occur in a single step starting with simple, readily available materials. As a result, great attention has been given to the development of multicomponent reactions (MCR)[1] because of their high degree of atom economy and their applications in combinatorial chemistry as well as diversity-oriented syntheses. Despite the intense interest in MCR, only a limited effort has been given to applying these processes to the synthesis of stereochemically complex polycyclic compounds.[2]

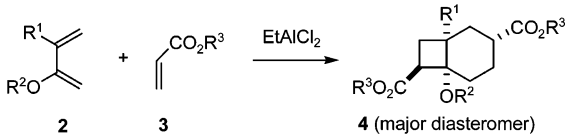
Recent studies in our laboratory have led to development of a hard Lewis acid (e.g., $EtAlCl_2$)-catalyzed, intermolecular Michael aldol-like, (2 + 2)-cycloaddition reaction.[3] The process affords substituted cyclobutanes starting with silyl enol ethers and α,β-unsaturated esters. In an extension of this work, we envisaged that a Lewis acid-promoted cascade process involving sequential Diels−Alder reaction and (2 + 2)-cycloaddition between 2-siloxydiene and α,β-unsaturated ester partners would provide complex polycyclic products (Scheme 1). In this communication, we describe the results of an investigation of this novel catalytic cascade (4 + 2)−(2 + 2) cycloaddition process, which leads to the construction of bicyclo[4.2.0]octanes, and its application to the synthesis of a substance reported to be the cytotoxic sesquiterpene paesslerin A (**1**) by Palermo and co-workers.[4]

Scheme 1



Initial optimization to carry out desired cascade (4 + 2)−(2 + 2) cycloaddition reactions showed that highest yields were obtained when 1 equiv of the siloxydiene, 4 equiv of the acrylate, and 0.5 equiv of $EtAlCl_2$ were used for 1 h reactions at −78 °C. When lesser amounts of either the acrylate or $EtAlCl_2$ were employed, incomplete reaction was observed. The results of the cascade (4 + 2)−(2 + 2) cycloaddition process are summarized in Table 1. Reaction of 2-*tert*-butyldimethyl-siloxybutadiene (**2a**) with methyl acrylate (**3a**) was found to afford a mixture of three diastereomeric trisubstituted bicyclo[4.2.0]octanes **4a** in 64% yield (entry 1). In contrast, reaction of the 3-methyl-2-siloxydienes **2b** and **2c** resulted in more efficient production of **4c** and **4d**, respectively (entries 3 and 4). The enhanced yields in these cases might be a result of the higher stabilities of the tetrasubstituted silyl enol ether intermediates. A slight improvement in diastereoselectivity was observed when triisopropylsiloxydiene **2c** was employed as a reactant (entries 5 and 6). The relative configuration of the major diastereomeric product **4e** was confirmed by using NMR spectroscopy.[5] The excellent levels of diastereoselectivity observed in these cascade reactions was likely a result of stereo-electronically controlled axial attack by acrylate in the second Michael aldol-like, (2 + 2)-cycloaddition step. The stereochemistry at the cyclobutyl ester center in the products was established in the final aldol addition process.[3]

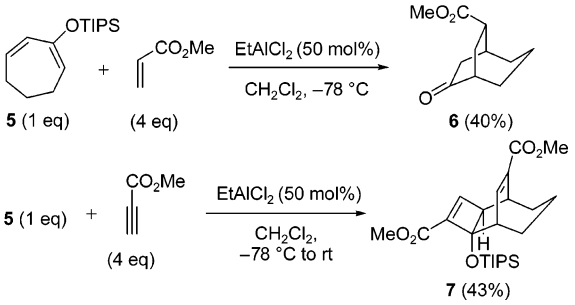
Table 1. Cascade (4 + 2)−(2 + 2) Cycloaddition[a]



entry	diene (R^1, R^2)	acrylate (R^3)	product	yield (%)	dr[b,c]
1	**2a** (H, TBS)	**3a** (Me)	**4a**	64	88:9:3
2	**2a**	**3b** ($CH(CF_3)_2$)	**4b**	66	88:12:0
3	**2b** (Me, TBS)	**3a**	**4c**	82	85:15:0
4	**2b**	**3b**	**4d**	79	91:9:0
5	**2c** (Me, TIPS)	**3a**	**4e**	79	94:6:0
6	**2c**	**3b**	**4f**	75	97:3:0

[a] Reaction conditions: **2** (1 equiv), **3** (4 equiv), 50 mol % $EtAlCl_2$, CH_2Cl_2, −78 °C, 1h. [b] Stereochemistry was not determined for the minor isomers. [c] Diastereomeric ratio was determined by ^1H NMR.

Scheme 2



To probe an application of this novel MCR to the preparation of the complex target, paesslerin A (**1**), cascade (4 + 2)−(2 + 2) cycloadditons of cyclic siloxydienes were investigated (Scheme 2). However, reaction of 2-siloxycycloheptadiene **5** with acrylate **3a** did not result in the formation of an MCR product even when it

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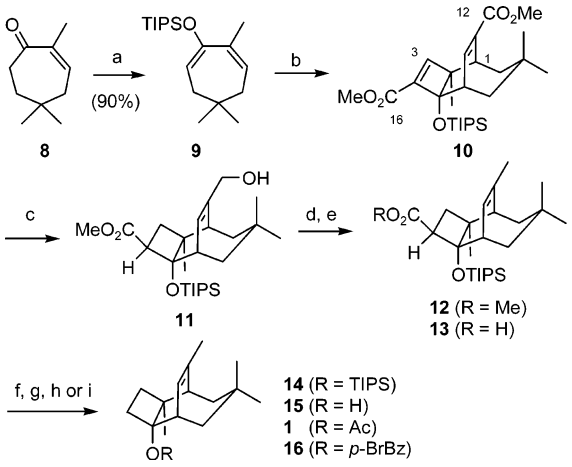
Scheme 3. Total Synthesis of **1**[a]



[a] Reagent: (a) TIPSOTf, NEt_3, −78 °C, 90%. (b) Methyl propiolate, $EtAlCl_2$, −40 °C to rt, 92%. (c) DIBAL-H (5 equiv), −78 °C, 74%. (d) ClCSOPh, Py, rt, then Bu_3SnH, AIBN, 80 °C. (e) *t*-BuOK, H_2O-THF, 70% for two steps. (f) HOTT,[10] Et_3N, DMAP, rt, then *t*-dodecanethiol, 85 °C. (g) TBAF, reflux, 81% for two steps. (h) Ac_2O, cat. $Sc(OTf)_3$, 99%. (i) For **15**, BuLi, rt, then *p*-bromobenzoyl chloride, 41%.

was conducted at higher temperature. In this case, the desilylated (4 + 2) adduct **6** was formed as a single diastereomer. A plausible explanation for this observation is that steric hindrance retards the second (2 + 2)-cycloaddition step. As expected, cascade (4 + 2)−(2 + 2) cycloaddition of **5** with methyl propiolate in the presence of $EtAlCl_2$ did take place to furnish tricyclo[4.3.2.$0^{2,5}$]undecane **7** as a single diastereomer. A higher temperature was required for this (2 + 2) cycloaddition reaction. 2D-NMR analysis revealed that the adduct **7** has the same relative stereochemistry as found in the substance reported to be paesslerin A (**1**).

The route for synthesis of paesslerin A (**1**), employing the novel cascade (4 + 2)−(2 + 2) cycloaddition process, is shown in Scheme 3. Siloxydiene **9** was prepared from the known enone **8**.[6] The key cascade reaction of **9** with methyl propiolate generated the tricyclic intermediate **10** in excellent yield (92%) and with complete diastereoselectivity. The relative stereochemistry of **10** was determined by using X-ray crystallography.[7] A critical issue in this sequence was regioselective reduction of **10** at the C-12 ester group. We anticipated that this would be favored over reduction at the C-16 ester because of steric crowding of the latter by the bulky triisopropylsiloxy group at C-5. In the event, treatment of **10** with DIBAL-H at −78 °C led to selective 1,2-reduction of the ester at C-12, accompanied by unexpected 1,4-reduction of the cyclobutene carboxylate to afford **11** in 74% yield.

Next, alcohol **11** was transformed into **12** by reductive dehydroxylation via the nonisolated intermediate xanthate.[8] Hydrolysis of the ester group in **12** to form **13** was followed by decarboxylation to generate **14** by using an improved Barton's method[9] employing HOTT.[10] Treatment of **14** with TBAF furnished alcohol **15**, which was converted into the proposed structure of paesslerin A (**1**) by using Sc-catalyzed acetylation.[11] The sequence for the synthesis of **1** from **8** was accomplished in 34% overall yield (eight steps).

Surprisingly, comparisons of the ^1H and ^{13}C NMR data of the synthetic compound with those reported for the natural product revealed that the substances are not identical. The 2D-NMR data for synthetic **1** are fully consistent with the structure of the target. Finally, the structure of synthetic **1** was unambiguously assigned by using X-ray crystallographic analysis of the derived *p*-bromobenzoate **16**.[13] The results clearly demonstrate that a revision of the structure of natural paesslerin A is required.

In conclusion, this study has led to the development of a novel cascade (4 + 2)−(2 + 2) cycloaddition, which allows for the rapid construction of polysubstituted bicyclo[4.2.0]octanes starting from three simple components. It is noteworthy that the MCR process is accompanied by formation of four carbon−carbon bonds and four stereogenic centers in a single operation. In addition, a short stereoselective synthesis of a substance proposed paesslerin A (**1**) has been accomplished.

Acknowledgment. We thank Dr. J. A. Palermo for his kind discussion about paesslerin A and Dr. C. Kabuto for crystallographic characterization. The work was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures, characterization data, observed NOESY correlations of **4e**, **7**, and **11**, and crystallographic structures of **10** and **16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For detailed NMR assignment of the major diastereomer of **4e**, see the Supporting Information. Stereochemistries of the other major isomer of **4** were inferred on the analogy of ^1H and ^{13}C NMR.

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(7) Crystal data for **10**. $C_{27}H_{44}O_5Si$, monoclinic, space group *C*2/*c*, a = 30.980(9) Å, b = 8.652(2) Å, c = 20.436(6) Å, β = 94.433(4)°, V = 5461.3(2) Å^3, Z = 8, D = 1.160 g/cm^3, R = 0.045, R_w = 0.112, GOF = 1.11.

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(10) Abbreviation of HOTT: *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouroniumhexafluorophosphate. Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732−5733.

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(12) Spectral data for synthetic **1**. Colorless oil, IR (neat) 1732 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ 5.69 (dt, 1H, J = 7.1, 1.8 Hz), 3.00 (t, 1H, J = 7.1 Hz), 2.17 (ddd, 1H, J = 14.3, 11.9, 7.7 Hz), 2.02 (s, 3H), 2.02 (ddd, 1H, J = 14.3, 10.1, 5.3 Hz), 1.82 (d, 3H, J = 1.8 Hz), 1.70 (d, 1H, J = 7.1 Hz), 1.55 (d, 1H, J = 14.9 Hz), 1.43 (ddd, 1H, J = 11.9, 11.4, 5.3 Hz), 1.43 (d, 1H, J = 14.9 Hz), 1.37 (ddd, 1H, J = 14.9, 7.1, 2.4 Hz), 1.26 (ddd, 1H, J = 11.4, 10.1, 7.7 Hz), 1.19 (s, 3H), 1.17 (ddd, 1H, J = 14.9, 7.1, 2.4 Hz), 0.96 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6, 141.5, 122.2, 85.3, 49.3, 45.3, 38.7, 36.7, 35.7, 35.6, 34.2, 31.8, 29.4, 28.6, 23.9, 21.8, 21.6, LRMS *m*/*z*: 262 (M^+).

(13) Crystal data for **16**. $C_{22}H_{27}BrO_2$, monoclinic, space group $P2_1/c$, a = 7.3901(8) Å, b = 12.005(1) Å, c = 22.278(5) Å, β = 91.6346(5)°, V = 1975.5(4) Å^3, Z = 4, D = 1.356 g/cm^3, R = 0.038, R_w = 0.040, GOF = 1.75.

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