Ring Contraction Strategy for the Practical, Scalable, Catalytic Asymmetric Synthesis of Versatile γ-Quaternary Acylcyclopentenes[**]

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Abstract

A simple protocol for the practical, scalable, catalytic asymmetric synthesis of γ-quaternary acylcyclopentenes in up to 91% overall yield and 92% ee has been developed. The reaction sequence employs a palladium-catalyzed enantioselective alkylation reaction and exploits the unusual stability of β-hydroxy cycloheptanones to achieve a general and robust method for performing two-carbon ring contractions. The resulting enantioenriched, highly-functionalized acylcyclopentenes provide a variable substituent and four additional functional group handles for chemoselective manipulation and potential application to the total synthesis of a wide array of natural products.

Keywords

ring contraction; rearrangement; allylic compounds; asymmetric catalysis; palladium; allylation; aldol reaction

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Highly substituted cyclopentanes are a common structural motif integrated into thousands of natural products.[1] Selected examples of bioactive compounds containing this basic structural unit include the hamigerans (**2**),[2a] steroids (**3**),[2b] pleuromutilin antibiotics (**4**),[2c] cyathane diterpenoids (**5**),[2d] cyclic botryococcenes (**6**),[2e] and anti-HBV schisanwilsonenes (**7a–c**)[2f] (Figure 1). Synthetic methods for the asymmetric preparation of cyclopentanoid cores with multiple functional group handles are highly desirable because they allow for the strategic synthesis of these and other natural products.[3] Toward this goal, we envisioned that functionalized chiral units such as acylcyclopentene **1** could serve

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as valuable synthetic intermediates (Figure 1). In this report, we describe a general and enantioselective preparation of versatile chiral acylcyclopentenes[4, 5] that combines a catalytic asymmetric alkylation reaction[6] and a facile two-carbon ring contraction.

Our work in this area began with observation of the unusual reactivity of seven-membered ring vinylogous esters compared to their six-membered ring counterparts. Although LiAlH$_4$ reduction of vinylogous ester **8** gave expected enone **9**[7] as the major product after acidic workup (Scheme 1A), subjecting the analogous seven-membered ring vinylogous ester (**10a**) to identical reaction conditions led to cycloheptenone **11a** as only a minor product (Scheme 1B). Interestingly, the major product was identified as stable β-hydroxyketone **12a**.[8] The lack of appreciable β-elimination even under acidic conditions suggests that subtle, but fundamental differences in ring conformational preferences between six- and seven-membered rings may lead to the strikingly different product distributions.[9]

To further examine the inherent reactivity of β-hydroxyketone **12a**, we exposed the compound to a variety of basic reaction conditions. Treatment of β-hydroxyketone **12a** with LiO*t*-Bu in *t*-BuOH afforded acylcyclopentene **1a** in 53% yield without any evidence of direct β-hydroxy elimination to enone **11a**. Overall, the reaction constitutes a two-carbon ring contraction that likely proceeds via a retro-aldol fragmentation/aldol cyclization pathway. Although isolated examples of the preparation of acylcyclopentenes from seven-membered rings[10] are known, general ring contraction methods have not been demonstrated with γ-quaternary stereocenters and catalytic asymmetric routes are unprecedented.

Enticed by this initial finding, we investigated the effect of different bases on product formation (Table 1). Alcohol additives in combination with LiOH in THF improved the yield for the reaction (entries 2–4), with CF$_3$CH$_2$OH[11] enabling the production of **1a** in 96% yield.[12] It is interesting to note that enone **11a** was not observed under any of the surveyed conditions. Among the conditions that promote the desired ring contraction, the combination of LiOH and CF$_3$CH$_2$OH in THF offered a mild, efficient, and selective method for further studies (entry 4).

With an optimized procedure for the ring contraction, we turned our attention to the asymmetric synthesis of various quaternary substituted vinylogous esters (e.g., **10**, Table 2).[13,14] A number of racemic β-ketoester substrates (e.g., **14**) for catalytic enantioselective alkylation could be obtained by acylation of parent vinylogous ester **13** with allyl cyanoformate[15] and trapping with a range of electrophiles under basic conditions.[16] Application of our standard enantioselective decarboxylative alkylation reaction conditions[6,13] to substrate **14a** produced chiral vinylogous ester **10a** in 91% yield and 88% ee (entry 1).[17,18] Substituents such as ethyl, benzyl, propargyl, homoallyl, and 2,4-pentadienyl were well-tolerated in the reaction, giving similarly high yields and enantioselectivity (entries 2–6). A number of heteroatom containing substrates were explored to test if more diverse functionality could be incorporated into our target acylcyclopentenes (entries 7–11). β-Ketoesters bearing a 2-chloroallyl substituent readily underwent the enantioselective alkylation reaction (entry 7). Gratifyingly, compounds that possess Lewis basic moieties readily furnished the desired products without complications (entries 8–9). Even indoles and free aldehydes could be incorporated into the cycloheptenone products (entries 10–11).

The chiral vinylogous esters (e.g., **10**) prepared above allowed us to examine the scope of the ring contraction reaction (Table 3). Substrate reduction with LiAlH$_4$ and base-promoted rearrangement of vinylogous esters bearing γ-alkyl substituents provided access to the corresponding acylcyclopentenes in excellent yields over the two-step protocol (entries 1–6).

The chloroallyl, nitrile, and indole-containing substrates could be transformed with similarly high yields using the same conditions (entries 7–8, 10). Alternatively, DIBAL allowed smooth conversion of vinylogous ester **10i** containing an *N*-basic pyridine (entry 9). Milder reduction under Luche conditions enabled facile conversion of silyl ether substrates (entries 11–12).[19] Furthermore, *trans*-propenyl substituted (entry 13) and spirocyclic (entry 14) substrates performed well in the ring contraction chemistry. With the combination of asymmetric alkylation and ring contraction, we achieved a route to substituted acylcyclopentenes with a wide range of functionality at the γ-quaternary stereocenter.

To demonstrate the practicality and scalability of the method, the α-methyl β-ketoester **14a** was converted to the corresponding acylcyclopentene **1a** in 69% yield over three steps on 15 g scale (Scheme 2A).[16] Notably, the multi-gram protocol proceeds with reduced catalyst loading and at higher reaction concentrations for the asymmetric alkylation step. Additionally, the enantiopurity of the acylcyclopentene **1a** can be increased to 98% ee by recrystallization of semicarbazone **15** (Scheme 2B).[16] Hydrolysis of hydrazone **15** with aqueous HCl enabled facile recovery of **1a**. Further derivatization afforded X-ray quality crystals of **16** for verification of absolute stereochemistry.[20] To enable access to β-substituted acylcyclopentenes, addition of *n*-BuMgBr to **10a** resulted in formation of tertiary β-hydroxyketone **17** (Scheme 2C).[16] Application of modified ring contraction conditions allowed access to acylcyclopentene **18**.

With a versatile, enantioselective synthesis of γ-quaternary acylcyclopentenes **1** in hand, we sought to demonstrate the further synthetic utility of these compounds. By combining site selective manipulations in short reaction sequences (1–4 steps), any of five reactive handles present in acylcyclopentene **1** can be functionalized (Scheme 3, sites **A**–**E**). Through careful implementation of these transformations, diverse monocarbocyclic (**1j**, **18–23**), spirocyclic (**24–25**), and fused polycyclic structures (**26–27**) can be obtained.[16]

In summary, we have developed a catalytic enantioselective synthesis for the preparation of densely functionalized chiral acylcyclopentenes in excellent yields and enantioselectivities. The protocol exploits a highly efficient Pd-catalyzed asymmetric alkylation reaction and a newly-developed, mild two-carbon ring contraction. The important chiral building blocks formed using this method can undergo a variety of synthetic transformations and will serve as valuable intermediates for the total synthesis of natural products. Efforts directed toward these ends are currently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. $Pd_2(pmdba)_3$ is preferable to $Pd_2(dba)_3$ in this reaction for ease of separation of pmdba from the reaction products during purification. dba = dibenzylideneacetone.

19. Exposure of aldehyde **10k** (Table 2, entry 11) to our standard reduction/ring contraction conditions produced a mixture of products as shown below:
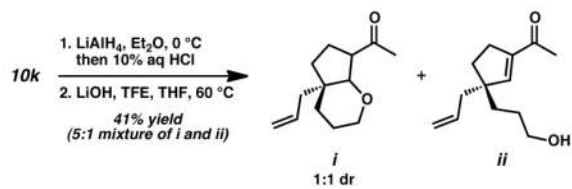
20. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 686849.
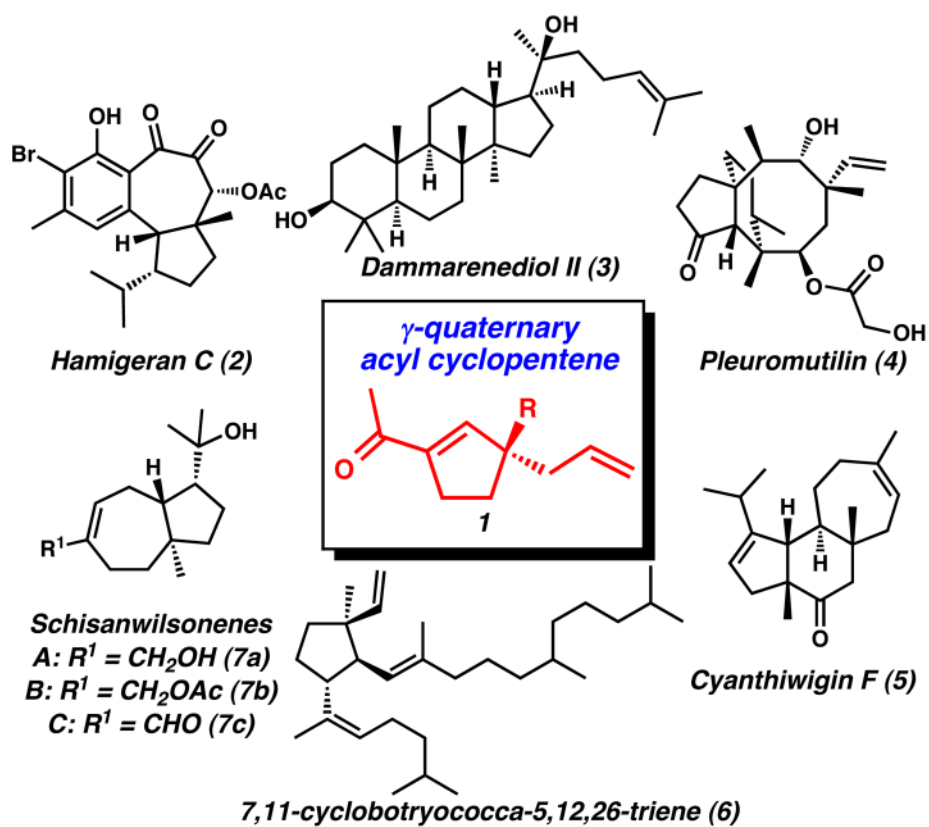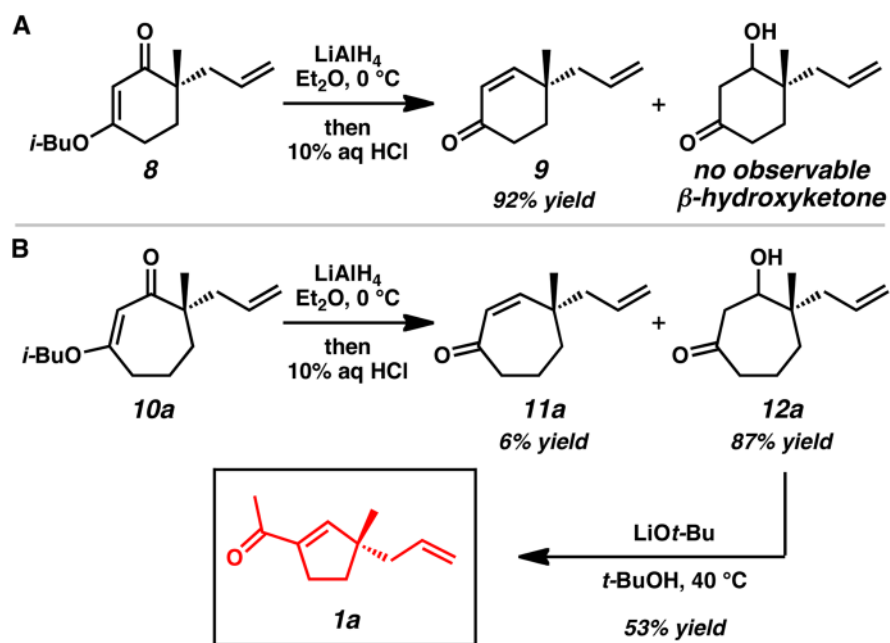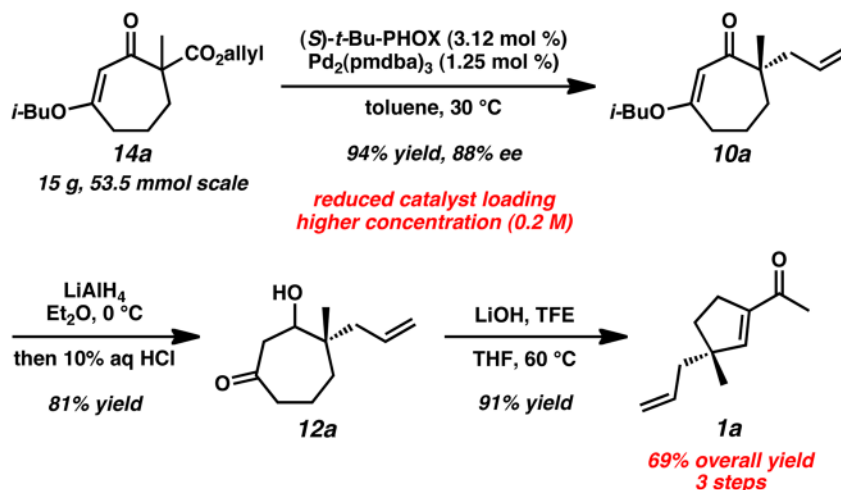
Figure 1.
Representative natural products possessing cyclopentanoid core structures with quaternary stereocenters.
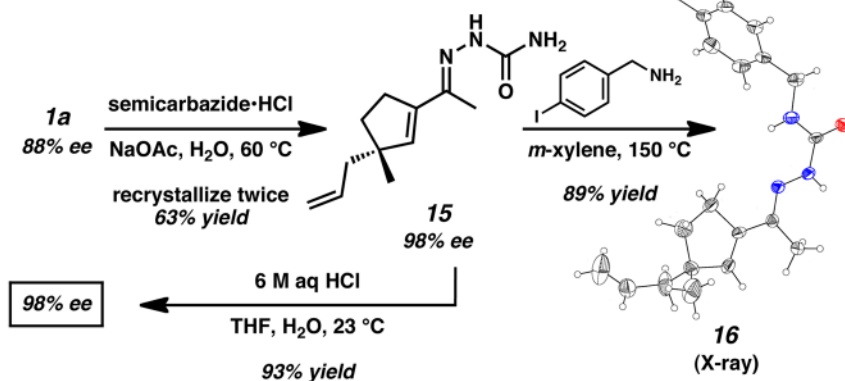
Scheme 1.
Anomalous reactivity of seven-membered ring vinylogous esters and discovery of a ring contraction reaction.
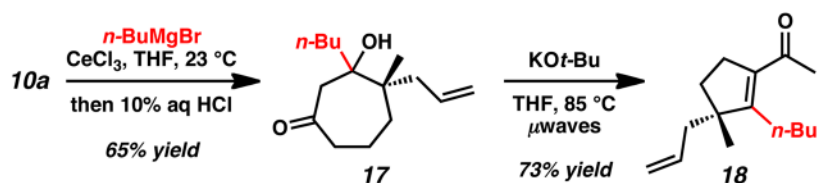
A. Ring Contraction Sequence on Multi-Gram Scale

14a
15 g, 53.5 mmol scale

(S)-t-Bu-PHOX (3.12 mol %)
Pd₂(pmdba)₃ (1.25 mol %)

toluene, 30 °C

94% yield, 88% ee

*reduced catalyst loading
higher concentration (0.2 M)*

10a

LiAlH₄
Et₂O, 0 °C

then 10% aq HCl

81% yield

12a

LiOH, TFE

THF, 60 °C

91% yield

1a

*69% overall yield
3 steps*

B. Enrichment of ee and X-ray Structure Determination

1a
88% ee

semicarbazide·HCl

NaOAc, H₂O, 60 °C

recrystallize twice
63% yield

15
98% ee

m-xylene, 150 °C

89% yield

16
(X-ray)

98% ee

6 M aq HCl

THF, H₂O, 23 °C

93% yield

C. Functionalization by Organometallic Addition

10a

n-BuMgBr
CeCl₃, THF, 23 °C

then 10% aq HCl

65% yield

17

KOt-Bu

THF, 85 °C
μwaves

73% yield

18

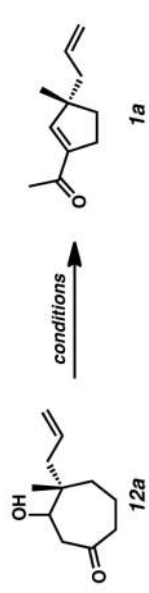**Scheme 2.**
Multi-gram ring contraction, enrichment of ee by recrystallization, and organometallic modified ring contraction sequence.
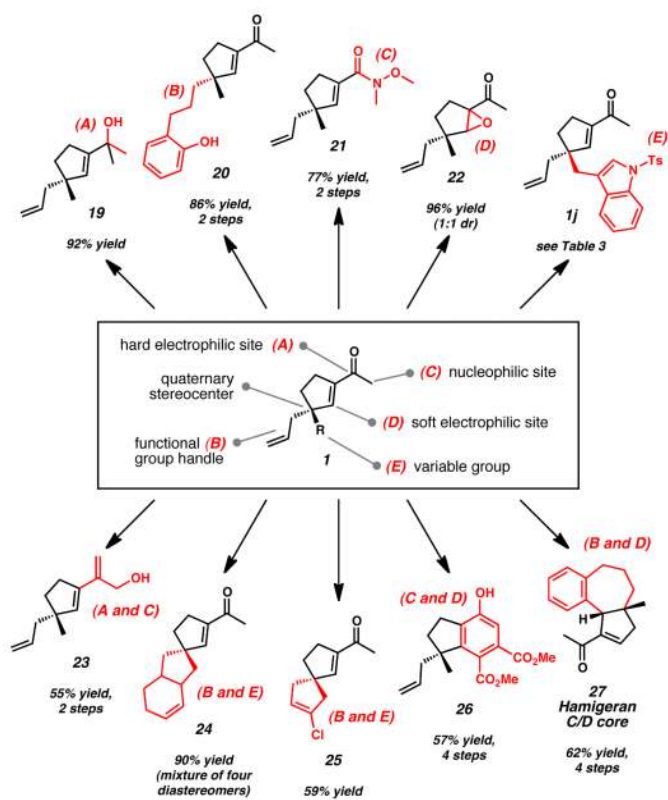
Scheme 3.
Versatility and synthetic utility of acylcyclopentenes.

Table 1

Ring contraction optimization.[a]

Entry	Base	Additive	Solvent	T [°C]	Yield [%][b]
1	LiO-t-Bu	none	t-BuOH	40	71 (53)[c]
2	LiOH	t-BuOH	THF	60	78
3	LiOH	HFIP[d]	THF	60	87
4	LiOH	CF$_3$CH$_2$OH	THF	60	96 (84)[c]

[a]Conditions: β-hydroxyketone (1.0 equiv), base (1.5 equiv), additive (1.5 equiv) in solvent (0.1 M) at indicated temperature for 9–24 h.

[b]GC yield using an internal standard.

[c]Isolated yield in parentheses.

[d]HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 2

Scope of the Pd-catalyzed enantioselective alkylation of cyclic vinylogous esters.[a]

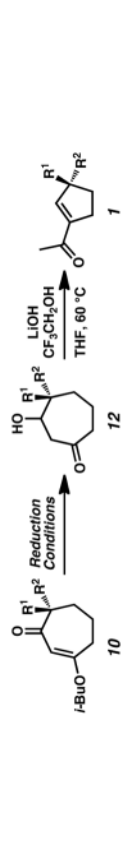| Entry	Substrate 14	R	Product 10	Yield [%][b]	ee [%][c]
1	14a	–CH₃	10a	91	88
2	14b	–CH₂CH₃	10b	89	92
3	14c	–CH₂Ph	10c	98	86
4	14d	–CH₂C≡CH	10d	88	89
5	14e	–CH₂CH₂CH=CH₂	10e	95	87
6	14f		10f	90	90
7	14g		10g	99	86
8	14h	–CH₂CH₂CN	10h	96	87
9	14i		10i	97	85
10	14j		10j	98	83
11	14k		10k	90	80

[a]Conditions: β-ketoester (1.0 equiv), Pd$_2$(pmdba)$_3$ (2.5 mol %), (*S*)-*t*-Bu-PHOX (6.25 mol %) in PhCH$_3$ (0.1 M) at 30 °C; pmdba = 4,4′-methoxydibenzylideneacetone.
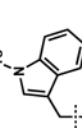
[b]Isolated yield.

[c]Determined by chiral HPLC or SFC.

Table 3

Ring contraction substrate scope.

Entry	Substrate 10	R^1	R^2	Product 1	Overall Yield [%][e]
1[a,d]	10a	–CH$_3$	–CH$_2$CH=CH$_2$	1a	84
2[a,d]	10b	–CH$_2$CH$_3$	–CH$_2$CH=CH$_2$	1b	90
3[a,d]	10c	–CH$_2$Ph	–CH$_2$CH=CH$_2$	1c	86
4[a,d]	10d	–CH$_2$C≡CH	–CH$_2$CH=CH$_2$	1d	95
5[a,d]	10e	–CH$_2$CH$_2$CH=CH$_2$	–CH$_2$CH=CH$_2$	1e	87
6[a,d]	10f		–CH$_2$CH=CH$_2$	1f	91
7[a,d]	10g		–CH$_2$CH=CH$_2$	1g	92
8[a,d]	10h	–CH$_2$CH$_2$CN	–CH$_2$CH=CH$_2$	1h	85
9[b,d]	10i		–CH$_2$CH=CH$_2$	1i	80
10[a,d]	10j		–CH$_2$CH=CH$_2$	1j	87
11[c,d,f]	10l	–CH$_2$OTBDPS	–CH$_2$CH=CH$_2$	1l	91
12[c,d,g]	10m	–(CH$_2$)$_3$OTBDPS	–CH$_2$CH=CH$_2$	1m	85

Entry	Substrate 10		Product 1		
		R[1]	R[2]	1	Overall Yield [%][e]
13[c,d,h]	10n		1n		81
14[a,d,g]	10o		1o		87

[a] *Reduction Conditions A:* vinylogous ester (1.0 equiv), LiAlH4 (0.55 equiv) in Et₂O (0.2 M) at 0 °C, then 10% aqueous HCl quench.

[b] *Reduction Conditions B:* 1) vinylogous ester (1.0 equiv), DIBAL (1.2 equiv) in PHCH₃ (0.03 M) at −78 °C; 2) oxalic acid•2H₂O in MeOH (0.02 M).

[c] *Reduction Conditions C:* vinylogous ester (1.0 equiv), CeCl₃•7H₂O (1.0 equiv), NaBH4 (3.0 equiv) in MeOH (0.02 M) at 0 °C, then 10% aqueous HCl in Et₂O at 0 °C.

[d] *Ring Contraction Conditions:* β-hydroxyketone (1.0 equiv), CF₃CH₂OH (1.5 equiv), LiOH (1.5 equiv) in THF (0.1 M) at 60 °C.

[e] Isolated yield over 2–3 steps.

[f] See Supporting Information for experimental procedures for substrate synthesis.

[g] Prepared from **14k**. See Supporting Information.

[h] Prepared from **14a**. See Supporting Information.