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Asymmetric synthesis of 2-alkyl-4-hydroxycyclohex-2-en-1-ones by scandium(III) triflate-catalyzed fragmentation of 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones

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ABSTRACT

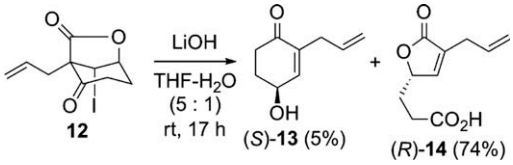
Fragmentation of (2*S*,3*S*,4*S*)-2-allyl-3-iodo-1-oxocyclohexan-2,4-carbolactone to (4*S*)-2-allyl-4-hydroxycyclohex-2-en-1-one, a chiral building block of (−)-platensimycin, proceeded efficiently by using scandium(III) triflate in DMF–H_2O (1:3) at 100 °C.

We have recently reported[1] a stereocontrolled formal synthesis of (±)-platensimycin (**1**):[2] a racemic caged compound **5**, Nicolaou's intermediate for the total synthesis of **1**,[3] was synthesized by using stereoselective Diels–Alder reaction between enone **2** and siloxydiene **3** to compound **4** as a key step (Scheme 1). Since all the stereocenters in **5** were controlled by the stereochemistry presented in **2**, the preparation of enantiomerically pure (*S*)-**2** is required for the asymmetric synthesis of (−)-**1**. Optically pure 2-alkyl-4-hydroxycyclohex-2-en-1-ones are important chiral building blocks in organic synthesis,[4] and a method for their efficient preparation needs to be developed.

Schultz et al. reported that LiOH-mediated hydrolysis of iodolactone **9**, which was prepared from chiral amide **8** by Birch reduction, alkylation,[5] hydrolysis, and iodolactonization, gave **6** as the major product only when R was the methyl group (**6**:**7** = 71:12, Scheme 2, path a).[6] Butenolide **7** was generally obtained as the major product when R was a substituent larger than the methyl group (path b). Therefore, it was expected that 2-allyl-4-hydroxycyclohexenone (**6**, R = allyl) would not be obtained efficiently by the basic hydrolysis of **9**, and it was thought that acid-catalyzed fragmentation of **9** might change the reaction course[7] and that **6** would be prepared effectively even when the substituent at the 2-position (R) was larger than the methyl group. Based on this idea, we found appropriate reaction conditions for the planned acid-catalyzed fragmentation of **9**–**6**, and we report here the results obtained in this research.

In order to synthesize optically pure (*S*)-**2**, which is a chiral building block for the synthesis of (−)-**1**, we employed chiral amide *ent*-**8** (Scheme 3). According to Schulz's procedure,[6] Birch reduction of *ent*-**8** followed by alkylation with 1-bromo-3-(phenylthio)propane gave **10** in 78% yield. Hydrolysis of the enol ether moiety with diluted hydrochloric acid, oxidation of the phenylthio group with *m*CPBA, and iodolactonization of the formed sulfoxide proceeded readily to afford iodolactone **11**. Elimination of the phenylsulfinyl group in refluxing xylene gave **12** in 76% yield, and the optical purity of **12** at this point was determined to be 89% ee by chiral HPLC. This result suggests that the diastereoselectivity for alkylation to **10** is 89% de. Optically pure **12** (>99% ee)[8] was obtained by recrystallization of **12** with cyclohexane.

As suggested in Schultz's report,[6] basic hydrolysis of **12** with LiOH in THF–H_2O (1:2) gave the desired product (*S*)-**13** only in 5% yield, and undesired butenolide carboxylic acid (*R*)-**14** was obtained as the major product (74% yield, Eq. 1):



(1)

Acid-catalyzed hydrolysis of **12** was then investigated by employing various Brønsted acids and Lewis acids in DMF–H_2O (1:3)[9] at 100 °C (Table 1). All the Brønsted acids and Lewis acids employed afforded the desired compound **13** as the major product.

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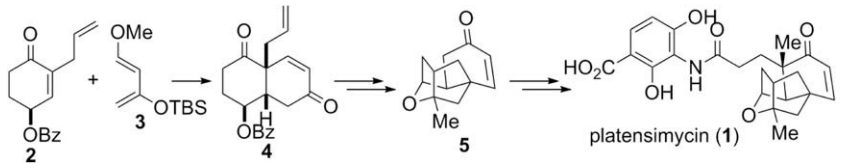
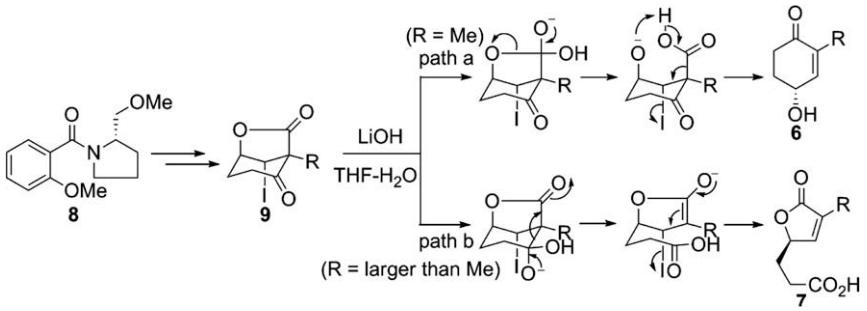
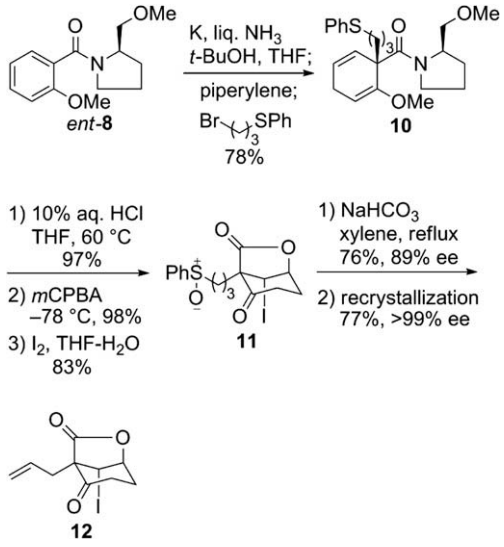


Scheme 1. Formal synthesis of (±)-platensimycin (**1**).



Scheme 2. Schultz and Khim's report on hydrolysis of **9** under basic conditions.[6b]

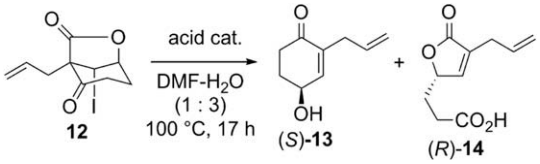


Scheme 3. Preparation of optically pure **12**.

It was found that $Sc(OTf)_3$[10] catalyzed the desired fragmentation most efficiently to afford (*S*)-**13** in 77% yield, and it was confirmed by chiral HPLC analysis that racemization did not take place in this step, and optically pure (*S*)-**13** (>99% ee) was formed (entry 4).[11] The fragmentation proceeded very slowly under catalysis with Brønsted acids such as sulfuric acid, TsOH, and TfOH, and most of starting materials were recovered in these cases (entries 1–3). Activation with $Ln(OTf)_3$ and $Yb(OTf)_3$ was also insufficient for smooth fragmentation of **12** to **13** (entries 5 and 6).

The scope and limitations of the present $Sc(OTf)_3$-catalyzed fragmentation of iodolactones **9** to 2-alkyl-4-hydroxycyclohex-2-en-1-ones **6** were examined (Table 2). The fragmentation of iodolactones **9a–c** having *n*-butyl, 3-phenylpropyl, and 3-(benzyloxy)propyl groups as R gave the corresponding 4-hydroxycyclohexenones **6a–c** as the major products, whereas fragmentation of iodolactone **9d** bearing a benzyl group as R gave butenolide **7d** as the major product. These results suggest that the present $Sc(OTf)_3$-catalyzed fragmentation of **9**–**6** proceeds smoothly when relatively linear groups are substituted as R at the 2-position of **9**.

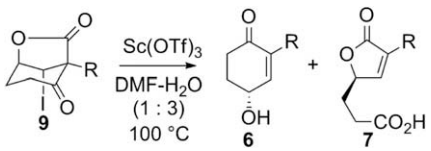
Table 1
Acid-catalyzed fragmentation of **12** to (*S*)-**13**[a]



Entry	Acid cat.	**13** (% yield[b])	**14** (% yield[b])
1[c]	H_2SO_4	18	0
2	TsOH	16	0
3	TfOH	13	0
4	$Sc(OTf)_3$	77	10
5	$La(OTf)_3$	18	6
6	$Yb(OTf)_3$	40	2

[a] One equivalent of acid catalysis was employed in DMF–H_2O (55 μM).
[b] Isolated yield.
[c] Sulfuric acid (0.5 equiv) was employed.

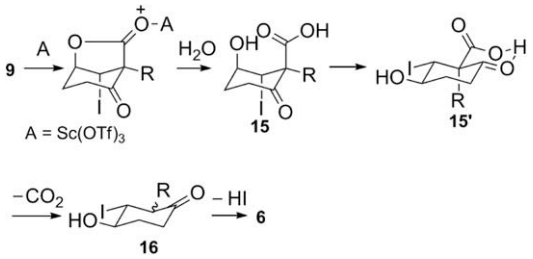
Table 2
$Sc(OTf)_3$-catalyzed fragmentation of **9**–**6**[a]



Entry	R	**9**	Time (h)	**6** (% yield[b])	**7** (% yield[b])
1	Bu	**9a**	23	**6a** (62)	**7a** (13)
2	$Ph(CH_2)_3$	**9b**	23	**6b** (53)	**7b** (7)
3	$BnO(CH_2)_3$	**9c**	21	**6c** (71)	**7c** (trace)
4	$PhCH_2$	**9d**	18	**6d** (17)	**7d** (56)

[a] One equivalent of $Sc(OTf)_3$ was employed in DMF–H_2O (55 μM).
[b] Isolated yield.

A proposed mechanism for $Sc(OTf)_3$-catalyzed fragmentation of **9**–**6** is shown in Scheme 4. Scandium triflate activates ester carbonyl group of **9**, and the γ-butyrolactone moiety is hydrolyzed to give hydroxy carboxylic acid **15**. Decarboxylation proceeds via



Scheme 4. Proposed mechanism for $Sc(OTf)_3$-catalyzed fragmentation of **9** to **6**.

a conformer **15′** in a concerted pathway to form iodo ketone **16**, and successive elimination of HI takes place to give **6**.

In summary, we established an efficient method for the preparation of (4*S*)-2-allyl-4-hydroxycyclohex-2-en-1-one ((*S*)-**13**) by $Sc(OTf)_3$-catalyzed fragmentation of iodolactone **12** in DMF-H_2O at 100 °C. Asymmetric synthesis of platensimycin (**1**) can be performed by employing thus-obtained (*S*)-**13**. The $Sc(OTf)_3$-catalyzed fragmentation is also useful for the preparation of other optically pure 2-alkyl-4-hydroxycyclohex-2-en-1-ones **6** from iodolactones **9**, which are readily prepared from chiral amide **8**.

Acknowledgments

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8. *(2S,3S,4S)-2-Allyl-3-iodo-1-oxocyclohexan-2,4-carbolactone* (**12**): mp 113.0–114.0 °C (cyclohexane); $[\alpha]_D^{26}$ +186.2 (*c* 0.744, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.39–2.52 (m, 2H), 2.59–2.82 (m, 4H), 4.71 (dd, *J* = 5.4, 1.7 Hz, 1H), 4.98–5.02 (m, 1H), 5.22 (like d, *J* = 10.0 Hz, 1H), 5.26 (dtd, *J* = 17.1, 9.8, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7, 27.5, 29.1, 33.0, 62.9, 77.6, 121.3, 130.6, 169.1, 197.6; IR ($CHCl_3$, cm^{-1}) 1786, 1730; Anal. Calcd for $C_{10}H_{11}IO_3$: C, 39.24; H, 3.62. Found: C, 39.20; H, 3.64.
9. Both the combination of DMF–H_2O and its ratio (1:3) were important for the fragmentation. The combinations such as THF–H_2O and *t*-BuOH–H_2O were not effective.
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11. *Experimental procedure*: The solution of **12** (99.5 mg, 0.33 mmol) and $Sc(OTf)_3$ (167.1 mg, 0.34 mmol) in DMF (1.5 mL) and H_2O (4.5 mL) was stirred at 100 °C for 17 h. After cooling to room temperature, H_2O was added, and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product purified by column chromatography on silica gel (hexane-ethyl acetate, from 3:1 to 1:1) gave (*S*)-**13** (38.2 mg, 0.25 mmol, 77%) as a colorless oil and (*R*)-**14** (6.2 mg, 32 μmol, 10%). (4*S*)-2-allyl-4-hydroxy-cyclohex-2-en-1-one ((*S*)-**13**): $[\alpha]_D^{24}$ −41.4 (*c* 0.400, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.90–2.01 (m, 1H), 2.29–2.45 (m, 3H), 2.62 (dt, *J* = 16.5, 6.1 Hz, 1H), 2.95 (like d, *J* = 6.7 Hz, 2H), 4.54–4.61 (br, 1H), 5.04–5.11 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 6.67–6.70 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.6, 33.0, 35.5, 66.6, 117.0, 134.8, 137.9, 148.0, 198.2; IR ($CHCl_3$, cm^{-1}) 1674, 1644; HRMS (EI) calcd for $C_9H_{12}O_2$: 152.08373; found 152.08380.