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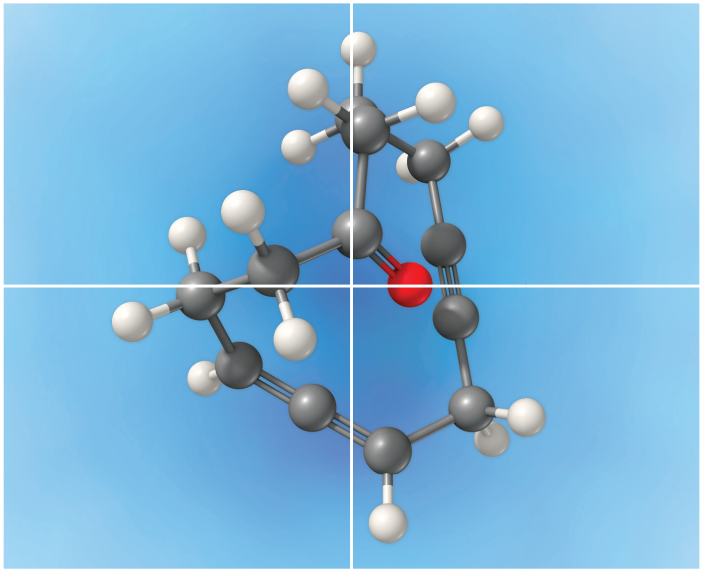

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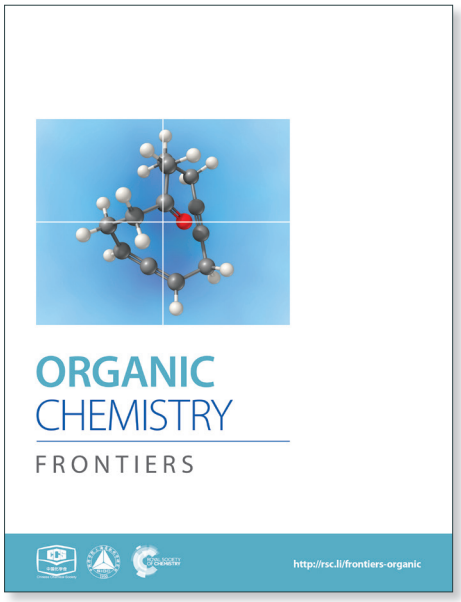

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A Concise Formal Synthesis of Platencin†

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A concise formal synthesis of platencin has been realized, featuring an organocatalytic approach to the [2.2.2] bicycli core, a radical reductive elimination, a Au-catalyzed Meyer-Schuster rearrangement and a Rh-catalyzed chemo- and diastereoselective hydrosilylation.

Platencin (**1**) and platensimycin (**2**) have been among the most prominent natural products in recent years. Identified by a team of Merck scientists from the strains of *Streptomyces platensis*, these two natural products exhibit broad-spectrum antibacterial activity against Gram-positive pathogens that show resistance to current antibiotics, including methycillin-, macrolide-, and linezolid-resistant *S. aureus*, vancomycin-resistant enterococci, and *Streptococcus pneumoniae*.[1,2] Platencin shows slightly stronger bioactivities than platensimycin, and blocks both FabF and FabH whereas platensimycin only inhibits the former.[2] In addition, platencin even as a racemic form exhibits potent bacteriostatic activities towards *Mycobacterium tuberculosis*.[3] Notably, the poor in vivo efficacy has precluded platencin itself from being a clinical drug.[4]

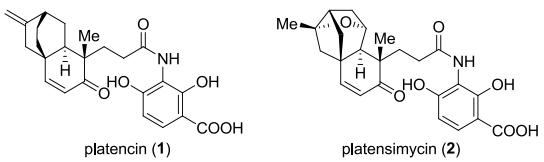
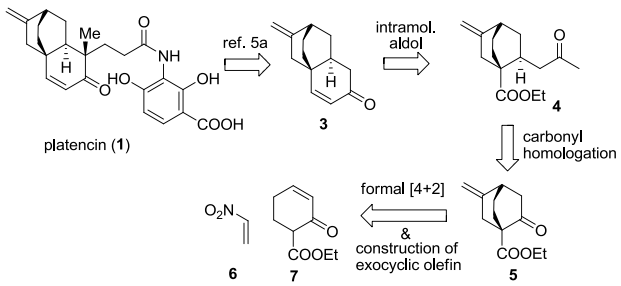


Fig. 1 Platencin (**1**), platensimycin (**2**).

Tremendous efforts have been exerted from the synthetic community resulting in numerous syntheses of platencin[5a-t] and its analogues.[5u-x] From a perspective of target oriented synthesis, Mulzer and Tiefenbacher's work stands out as the most efficient synthesis of platencin so far.[5c] Nevertheless, synthetic endeavors based on new strategies are still highly desirable. Recently, we successfully developed a convenient approach to bicyclo[2.2.2]octane-1-carboxylates.[6] In this paper, we report a formal synthesis of platencin by virtue of this new method.

Our retrosynthesis is depicted in Scheme 1. Nicolaou's intermediate enone **3** was chosen as the direct synthetic target.[5a] Enone **3** could be reduced to dicarbonyl **4**, which in turn could be traced back to **5**. Eventually, in light of our methodology, a formal [4+2] cycloaddition reaction of nitroethylene (**6**) with α'-ethoxycarbonyl cyclohexenone (**7**) was envisaged to access **5**.



Scheme 1 Retrosynthetic analysis of platencin (**1**).

Our synthesis commenced with the critical [4+2] reaction of **6** and **7** (Scheme 2). Surprisingly, by employing the original conditions involving **CAT-1** as the catalyst and dichloromethane as the solvent,[6] only trace amount of **8** could be isolated, probably as a result of the high propensity of **6** undergoing polymerization under the reaction conditions. To our delight, when toluene was used as the solvent and **6** was slowly introduced to the reaction mixture, the polymerization of **6** could be significantly suppressed, with **8** being isolated in 74% yield, albeit with an enantioselectivity of only 15% ee which could be ascribed to the absence of any substituent at the β-carbon of **6**.

A tandem Michael-Henry reaction was then realized with DBU and formaldehyde, providing **9** as a 1/1 diastereomeric mixture, which without chromatographic purification was brominated with PPh_3/CBr_4 to furnish **10** in 89% overall yield spanning three steps from **8**. The subsequent unprecedented conversion of **10** to **5** was examined with various reducing agents (Table 1). The optimal set of conditions involving n-Bu_3SnH/AIBN in heated toluene provided **5** in 91% yield.

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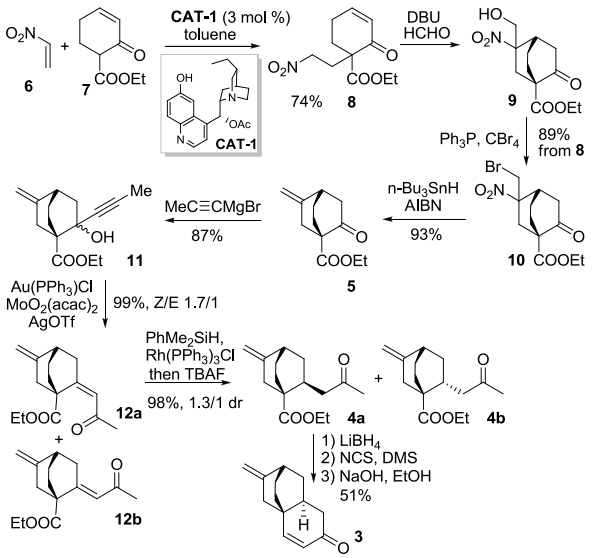
With a robust protocol established for the synthesis of **5**, we proceeded to the next synthetic stage. The Grignard addition of propargylmagnesium bromide to ketone **5** afforded **11** in 87% yield as a 1.5/1 mixture. The subsequent Au-catalyzed Meyer-Schuster rearrangement of **11** proved highly efficient.[7] With 2 mol % catalyst in dichloromethane, enone **12** could be obtained in a quantitative yield as a 1.7/1 mixture favouring the (*Z*)-isomer **12a**.[8] The chemo- as well as diastereoselective hydrogenation of **12a** was investigated (Table 2). A nearly quantitative yield of **4a** and its epimer **4b** in 1.3/1 ratio could be obtained by rhodium catalyzed hydrosilylation (entry 3).[8] Compared to the result obtained with *t*-BuCu/DIBAL-H (entry 2), the interaction between the exocyclic terminal double bond and the rhodium catalyst probably overrode the adverse inherent steric facial bias, leading to **4a** as the major product. Eventually, ketoester **4a** was subjected to the reduction-oxidation sequence to provide ketoaldehyde before undergoing the intramolecular aldol condensation to give enone **3** in 51% yield over three steps.



Scheme 2 Synthesis of **3**.

Table 1 Conditions screening for the conversion of **10** to **5**.

Entry	Conditions	Yield%
1	Mg, THF, 40 °C	21
2	Zn, NaI, MeOH, 50 °C	25
3	Zn, NH_4Cl, MeOH, r.t.	-
4	SmI_2, r.t.	-
5	*t*-BuLi, -78 °C	-
6	AIBN, *n*-Bu_3SnH, toluene, 90 °C	93

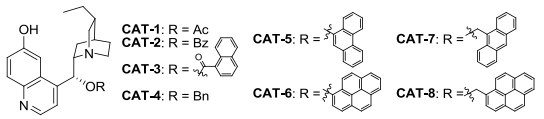
Table 2 Conditions screening for the chemo- and diastereo-selective reduction of **12a** to **4a/4b**.

Entry	Conditions	Yield%	dr
1	Raney Ni, H_2O, r.t.	-[a]	-
2	*t*-BuCu, DIBAL-H, -78 °C	-	1/4
3	$PhMe_2SiH$, $Rh(PPh_3)_3Cl$, 60 °C	98	1.3/1

[a] The terminal olefin was saturated first giving a complex mixture.

In view of the fact that the enantioselectivity of the initial key reaction delivering **8** was poor, we continued to improve the reaction by screening more catalysts and conditions, as summarized in Table 3. When **6** was dissolved in toluene and introduced slowly in excess, dichloromethane could be employed as the solvent which resulted in a slightly higher ee of 38% with reversed sense of enantioselectivity as compared to that obtained with toluene (entries 1 and 2). Lower temperature resulted in significantly decreased reactivity (entry 3). Further investigation of the catalysts revealed **CAT-5** to be the optimal one (entries 4~10). The best result was obtained with **CAT-5** in nitrobenzene, which furnished **8** in 84% yield and 74% ee (entry 12).

Table 3 Conditions screening for the production of **8**.



Entry	Catalyst	Conditions [a]	Conv.% [b]	ee% [c]
1	**CAT-1**	Toluene, r.t.	95	15
2	**CAT-1**	DCM, r.t.	72	-38
3	**CAT-1**	DCM, -20 °C	33	-42
4	**CAT-2**	DCM, r.t.	55	-42
5	**CAT-3**	DCM, r.t.	56	-41
6	**CAT-4**	DCM, r.t.	45	-52
7	**CAT-5**	DCM, r.t.	88	-72
8	**CAT-6**	DCM, r.t.	71	-63
9	**CAT-7**	DCM, r.t.	32	-68
10	**CAT-8**	DCM, r.t.	50	-65
11	**CAT-5**	PhCN, r.t.	94	-73
12	**CAT-5**	$PhNO_2$, r.t.	98 [d]	-74

[a] A solution of nitroethylene (**6**) in toluene (2.0 M) was always employed in excess. [b] Determined by analysis of the ^{1}H NMR of crude samples. [c] Determined by chiral HPLC analysis. [d] 84% isolated yield.

Conclusions

In conclusion, we have accomplished a concise formal synthesis of platencin, featuring an organocatalytic approach to the bicyclo[2.2.2]octane core, a radical reductive elimination, an efficient Au-catalyzed Meyer-Schuster rearrangement, and a Rh-catalyzed chemo- and diastereoselective hydrosilylation. The formal synthesis covers ten steps from simple starting materials with a good overall yield. Importantly, this synthesis demonstrates a new synthetic strategy that may readily lend itself to access to novel platencin analogues valuable for relevant drug discovery. Synthetic endeavours along this line are currently underway in our laboratory and will be reported in due course.

Acknowledgements

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8 See the Supporting Information for details.