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Enantioselective Modular Synthesis of Cyclohexenones: Total Syntheses of (+)-Crypto- and (+)-Infectocaryone

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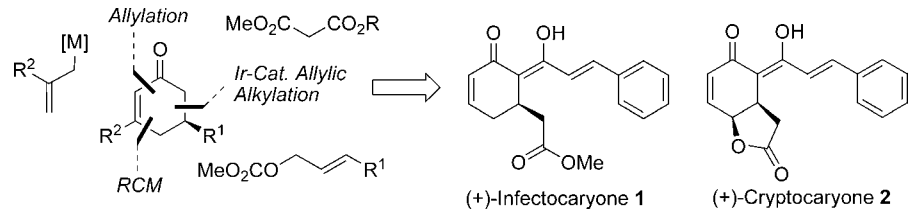
ABSTRACT



A modular synthesis of cyclohexenones is described and applied to the first enantioselective total syntheses of (+)-crypto- and (+)-infectocaryone. Key steps in the synthesis of cyclohexenones are an iridium-catalyzed allylic alkylation, nucleophilic allylation, and ring-closing metathesis. On the way to (+)-cryptocaryone, a catch and release strategy involving an iodolactonization/elimination and a regioselective C-acylation were used.

Enantiomerically pure cyclohexenones are versatile building blocks for the synthesis of natural products.[1] Their EPC (enantiomerically pure compound) synthesis has been carried out by ex-chiral pool approaches,[1,2] using terpenes such as pulegone or carvone as starting materials, and by asymmetric synthesis.[3] We herein present a novel modular synthesis of cyclohexenones and its application in the first enantioselective total syntheses of (+)-infecto- (**1**) and (+)-cryptocaryone (**2**).

Our method comprises an iridium-catalyzed allylic alkylation as the enantiodiscriminating step, expected to proceed with ee of >96%,[4] decarboxylation, reduction to an aldehyde, nucleophilic allylation, and ring-closing metathesis (RCM) to give a cyclohex-3-enone (Figure 1).[5] The ee of the product can be considerably improved if an asymmetric allylation, e.g., Brown allylation,[6] is employed. Cyclohex-3-enones are valuable because addition reactions at the double bond, for

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(3) (a) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811–814. (b) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807–6808. (c) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317. (d) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928–4930. (e) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656–7658.

(4) Reviews: (a) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, A., Claver, C., Eds.; Wiley-VCH: Weinheim, 2009; pp 211−250. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691. (c) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641–1655. (d) Takeuchi, R. *Synlett* **2002**, 1954–1965.

(5) For a related strategy for the synthesis of cyclopentenones see: (a) Schelwies, M.; Dübon, P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2466–2469. (b) Dübon, P.; Schelwies, M.; Helmchen, G. *Chem.—Eur. J.* **2008**, *14*, 6722–6733.

(6) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (b) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9–24. (c) Racherla, U. S.; Brown, C. H. *J. Org. Chem.* **1991**, *56*, 401–404. (d) Murga, J.; Garcia-Fortanet, F.; Carda, M.; Marco, J. *J. Org. Chem.* **2004**, *69*, 7277–7283.

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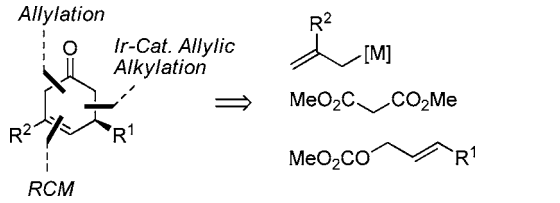
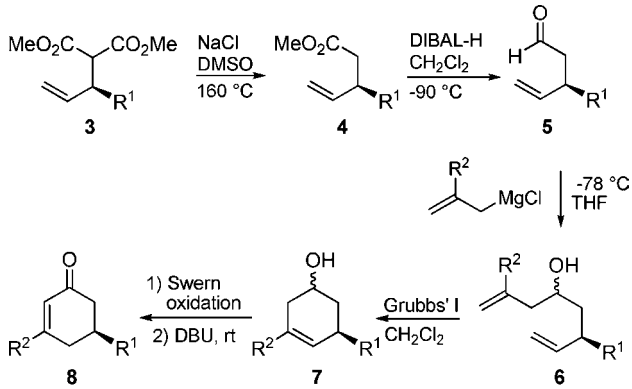


Figure 1. Modular enantioselective synthesis of cyclohexenones.

example, epoxidation or aziridination, are expected to proceed with high degrees of diastereoselectivity, and subsequent treatment with base yields γ-substituted α,β-unsaturated ketones. This catch and release strategy was employed in the synthesis of (+)-cryptocaryone (**2**).

In the first stage of this project, we have prepared the cyclohexenones **8a**−**8d** from the allylic alkylation products **3a**−**d** (Scheme 1). Synthesis of the latter with ee of ≥96%

Scheme 1. Modular Synthesis of Cyclohexenones



*Total yield (from **3**) and ee for*
8a: 53% (ee = 96%)
8b: 58% (ee = 98%)
8c: 47% (ee = 96%)
8d: 34% (ee = 98%)

3-8 a	$R^1 = CH_2OCPh_3$	R^2 = H
b	$R^1 = CH_2OCPh_3$	R^2 = Me
c	$R^1 = CH_2CH_2OCPh_3$	R^2 = H
d	R^1 = *n*-Pr	R^2 = Me

by iridium-catalyzed allylic alkylation has previously been described.[7] All of the cyclohexenones were prepared in high enantiomeric excess and excellent overall yield on a multigram scale. The route is advantageous, particularly for the synthesis of cyclohexenones with substituents in the 3-position.[2b] The ketone **8d**, also known as celery ketone, is used in its racemic form as a synthetic fragrance with typical lovage and celery character. We have prepared the (*S*)- as well as the (*R*)-enantiomer. These compounds have recently been characterized with respect to olfactory properties.[3e]

Next, we focused on asymmetric total syntheses of infectocaryone (**1**) and the related cryptocaryone (**2**) using the cyclohexene **9** as key intermediate (Figure 2). Infectocaryone (**1**) has not yet been synthesized; for (+)-crypto-

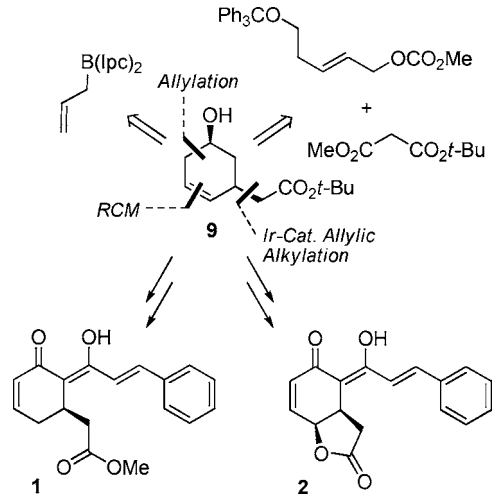


Figure 2. Retrosynthetic analysis.

caryone (**2**) a chiral auxiliary based synthesis has recently been reported.[8] (+)-Cryptocaryone was first isolated from the roots of *Cryptocarya bourdilloni* in 1972, and its structure was established in 1985.[9,10] (+)-Infectocaryone was isolated from the trunk bark of *Cryptocarya infectoria* in 2001.[11a] Both compounds display activity against KB cell lines,[11] with IC_{50} values of 1.7 μM for **1** and 1.8 μM for **2**. In addition, **2** was found to be cytotoxic against erythroleukemic K562 and doxorubicin-resistant K562 cells at an IC_{50} value of 2 μM.[11a]

The synthesis of the key intermediate **9** with ee of >99% started with an iridium-catalyzed allylic alkylation of the allylic carbonate **10**. Substrates with alkoxyalkyl or silyloxyalkyl substituents can give rise to relatively low levels of regioselectivity upon use of the standard catalysts derived from $[Ir(cod)Cl]_2$.[12] With our new catalyst system based on $[Ir(dbcot)Cl]_2$, improved regioselectivities are generally obtained.[7a] The branched product **11** was formed with excellent regioselectivity of b/l = 97:3 (Scheme 2), while the cod complex induced a regioselectivity of only b/l = 84:16.

Subsequent saponification/decarboxylation, O-deprotection, and Dess−Martin oxidation gave the aldehyde **13** in

(7) For **3a**−**c** see: (a) Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew* **2008**, *47*, 7652–7655. For **3d** see: (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529–3532.

(8) Fujioka, H.; Nakahara, K.; Oki, T.; Hirano, K.; Hayashi, T.; Kita, Y. *Tetrahedron Lett.* **2010**, *51*, 1945–1946.

(9) Govindachari, T. R.; Parthasarathy, P. C. *Tetrahedron Lett.* **1972**, *13*, 3419–3420.

(10) Parthasarathy, P. C. *Tetrahedron Lett.* **1985**, *26*, 5491–5492.

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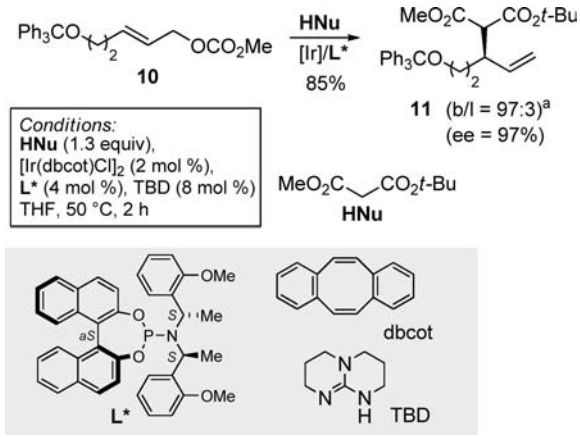
(13) The corresponding allylation with allyl magnesium chloride was not chemoselective.

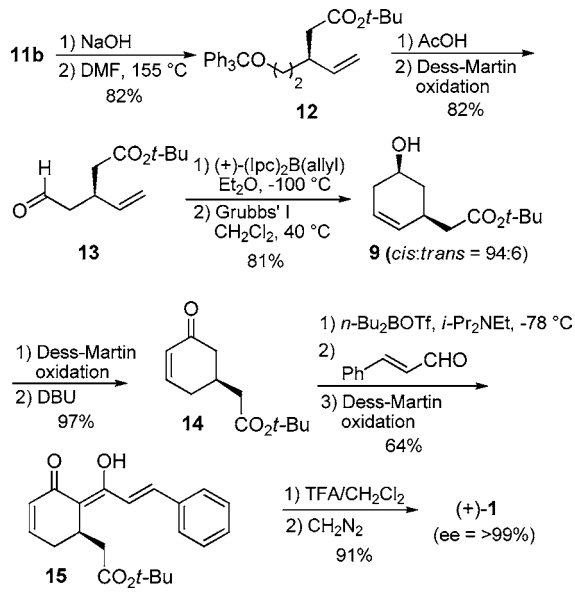
Scheme 2. Iridium-Catalyzed Allylic Alkylation



[a] b/l = branched product/linear product.

good yield (Scheme 3). Brown allylation[13] followed by ring-closing metathesis (RCM) furnished the cyclohexene **9** as a

Scheme 3. Synthesis of (+)-Infectocaryone (**1**)

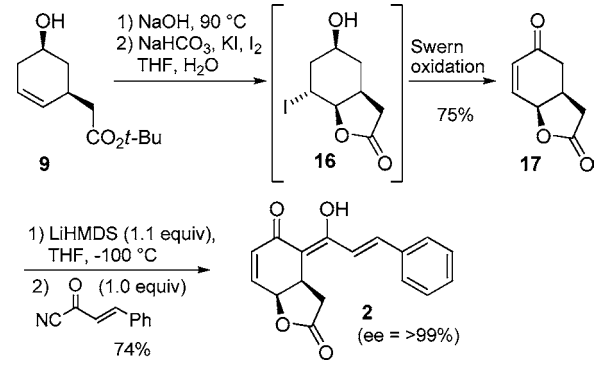


mixture of the *cis*- and the *trans*-diastereoisomers in a ratio of 94:6. The minor *trans*-diastereoisomer was separated off by column chromatography. The ester *cis*-**9** was obtained with very high ee of >99% (HPLC) because of double diastereoselection in the two asymmetric syntheses leading to it.

(+)-Infectocaryone (**1**) was synthesized from **9** in five steps as follows. Oxidation of **9** to the ketone and isomerization of the double bond with base gave the α,β-unsaturated ketone **14** in excellent yield. The second side chain was introduced by an aldol reaction with *trans*-cinnamaldehyde. The enolate produced with *n*-Bu_2BOTf gave excellent results,[14] while reactions with lithium enolates (LDA or LiHMDS) were poorly reproducible. Subsequent Dess−Martin oxidation gave enone **15** in 64% yield. Preparation of **15** by direct acylation of **14** with a cinnamoyl derivative was also achieved (see below). Finally, ester cleavage with TFA and reesterification with diazomethane furnished analytically pure (+)-infectocaryone (**1**) in 91% yield; its spectral data were in agreement with those reported for the natural product.[11a]

The completion of the total synthesis of (+)-cryptocaryone (**2**) was straightforward in the first part, but more challenging than anticipated in the final stage (Scheme 4). According to

Scheme 4. Synthesis of (+)-Cryptocaryone (**2**) via a Catch and Release Strategy



the catch and release strategy, the ester **9** was saponified and the resulting carboxylic acid was subjected to an iodolactonization reaction to give the lactone **16**. Swern oxidation effected both generation of the carbonyl group and elimination of HI to give the crystalline enone **17** in good overall yield.[15]

Next a selective C-acylation of **17** had to be realized to yield (+)-cryptocaryone (**2**). Attempts to perform an aldol reaction with cinnamaldehyde followed by oxidation, as in the synthesis of **1**, did not lead to the desired product. We decided to explore a direct acylation of an enolate of **17**. A screening with respect to both bases for enolate generation as well as acylating agents was performed (Table 1).

As acylating agents, activated acyl derivatives were tested that had been used in C-acylation reactions of enolates before: cinnamoyl chloride,[16] cinnamoyl cyanide,[17] *N*-(cinnamoyl)-imidazole,[18] and *N*-(cinnamoyl)-benzotriazole[19] (Table 1). Enolate formation required close attention, because the enolates of **17** were found to be unstable if deprotonation times exceeding 30 min at −78 °C were employed. Eventually, LiHMDS was identified as suitable base. Trials were

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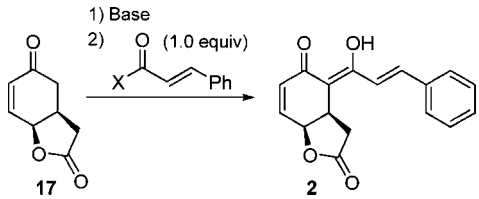
(15) The lactone **17** was characterized by crystal structure analysis. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 776574 contains the supplementary crystallographic data.

(16) Casey, M.; Donnelly, J. A.; Ryan, J. C.; Ushioda, S. *Akrivoc* **2003**, *vii*, 310–327.

Table 1. Reagent Screening for C-Acylation of **17**



entry	X	conditions deprotonation	conditions acylation	yield of **2** (%)
1	Cl	LiHMDS (1.1 equiv), THF, 10 min, -78 °C	15 min at -78 °C	26
2		LiHMDS (1.05 equiv), THF, 45 min, -78 °C	3 h at -78 °C	-
3		LDA (1.0 equiv), THF, 30 min, -78 °C	20 h at -78 °C	-
4		LiHMDS (1.05 equiv), THF, 55 min, -78 °C	3 h at -78 °C	18
5		LiHMDS (1.05 equiv), DME, 15 min, -78 °C	3 h at -78 °C	27
6	CN	LiHMDS (1.1 equiv), THF, 55 min, -78 °C	30 min at -78 °C	39
7	CN	LiHMDS (1.1 equiv), THF, 10 min, -78 °C	5 min at -78 °C	47
8	CN	LiHMDS (1.1 equiv), THF, 20 min, -100 °C	30 min at -100 °C	74

also performed with LDA, NaHMDS (decomposition), KO*t*-Bu, and Schwesinger base (phosphazene base P_1-*t*-Bu)[20] (no reaction). The combination of enolate formation with LiHMDS and reaction of the enolate with cinnamoyl cyanide at −100 °C gave (+)-cryptocaryone (**2**) in a yield of 74%.

The acylation procedure was also effective in the synthesis of (+)-infectocaryone (**1**); using conditions according to entry 7 of Table 1, the reaction of ketone **14** with cinnamoyl cyanide produced the enone **15** in 76% yield.

In summary, we are reporting a modular asymmetric synthesis of substituted cyclohexenones, which was applied in the first enantioselective total syntheses of (+)-cryptocaryone (**2**) and (+)-infectocaryone (**1**) (total yields of 26% and 32%, respectively). Key steps are iridium-catalyzed allylic alkylations with an improved catalyst based on dbcot as dienylic ligand, iodolactonization/elimination reactions in catch and release fashion, and a chemoselective C-acylation.

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Supporting Information Available: Experimental details including spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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