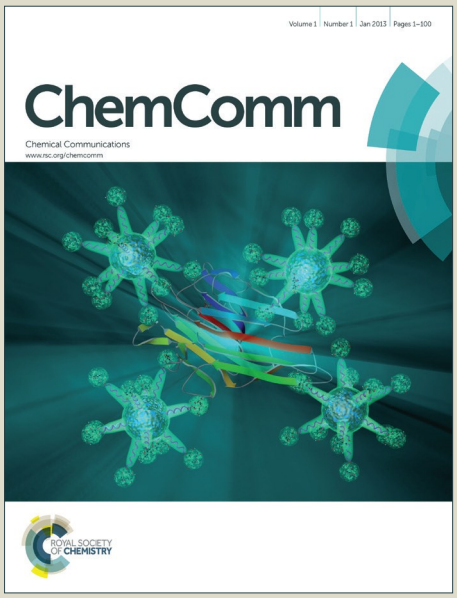
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: F. Horeischi, C. Guttroff and B. J. Plietker, *Chem. Commun.*, 2014, DOI: 10.1039/C4CC09701G.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Dynamic Article Links ▶
View Article Online
DOI: 10.1039/C4CC09701G

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

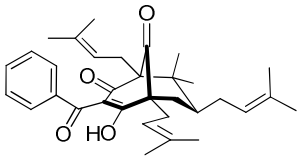
The Enantioselective Total Synthesis of (+)-Clusianone

Fiene Horeischi,[a] Claudia Guttroff,[a] and Bernd Plietker*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

(+)-Clusianone, an *exo*-type B PPAP with reported anti-HIV and chemoprotective activities, was synthesized within eleven steps with 97 % ee starting from acetylacetone. An enantioselective decarboxylative Tsuji-Trost-allylation plus a Ru-catalyzed ring-closing metathesis-decarboxylative allylation were used to control both diastereo- and enantioselectivity.

Within the past eight years reports on the isolation[1] and total synthesis[2-4] of polyprenylated polycyclic acylphloroglucinols (PPAP), a class of natural products consisting of more than 200 members with an unusual bicyclo[3.3.1]nonatrione core, have been published. The broad range of biological activities and the challenge to synthesize a product that, apart from its unusual bicyclic structure, is densely substituted possessing only three hydrogen atoms but up to four stereocenters (a minimum of up to three of them are quarternary), spurred the interest in developing new or evaluating existing methodologies. As a consequence elegant approaches toward *endo*-[5] and *exo*-type[6-10] PPAPs were accomplished by various groups. However, only a few enantioselective total synthesis are published up to date. Apart from the use of chiral auxiliaries[11], substituents[12], or reagents[13] only a few strategies that rely on asymmetric catalysis were reported.[14] Herein we describe a short total synthesis of (+)-clusianone in which an enantioselective decarboxylative Tsuji-Trost allylation[15,16] was used as a key-step (Figure 1).



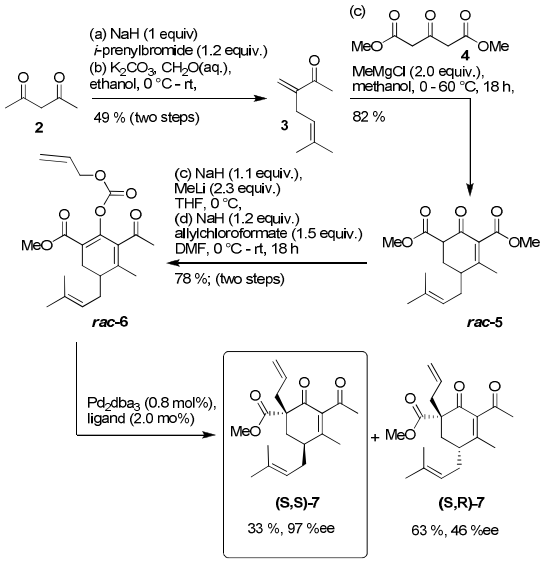
1

Figure 1. (+)-Clusianone.

(+)-Clusianone was isolated from *C. congestiflora* and shows interesting antiviral activities against HIV- and Eppstein-Barr virus infections. In particular the latter activity is interesting since the inhibition of this virus is discussed as a key-strategy in the field of chemoprotection.[17] The challenging scaffold and the reported bioactivities in combination with the difficulties to isolate bigger amounts of natural (+)-clusianone spurred our interest in developing a short total synthesis toward this interesting natural product.

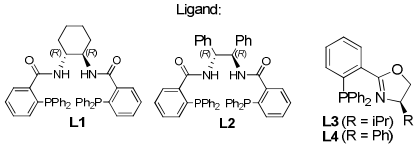
Starting from acetylacetone cyclohexenenone ***rac*-5** was obtained within three steps using the previously established transformations (Table 1).

Table 1. Preparation of enantiomerically enriched cyclohexenone (*S*,*S*)-**6**.



entry[a]	ligand[b]	solvent	time [h]	yield [%] (*trans*:*cis*)[c]	*ee* [%] (*trans*)[d]	*ee* [%] (*cis*)[d]
1	**L1**	THF	1	97 (84 : 16)	15	72
2	**L1**	toluene	1	93 (73 : 27)	34	90
3	**L1**	**pentane**	**1**	**95 (66 : 34)**	**46**	**97**
4	**L2**	pentane	24	93 (73 : 27)	29	82
5	**L2**	toluene	24	85 (72 : 28)	38	84
6	**L3**	THF	0.5	97 (100 : 0)	0	-
7	**L4**	THF	0.5	89 (100 : 0)	0	-

[a] All reactions were performed on a 0.125 mmol-scale under N_2-atmosphere until full conversion. [b] Ligand structures:

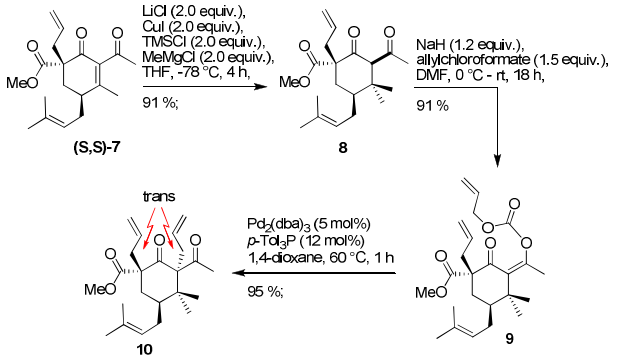


[c] Isolated yield, *trans-cis* ratio determined by ^{1}H NMR-integration of the crude product. [d] Determined by chiral HPLC.

View Article Online
DOI: 10.1039/C4CC09701G

Cyclohexenone ***rac*-5** was subsequently transferred into the corresponding allylvinylcarbonate **rac-6** which was subjected to the decarboxylative Tsuji-Trost allylation. A variety of chiral ligands were evaluated amongst which diaminocyclohexane derived ligand **(*R,R*)-L1** proved to be the optimum. The corresponding allylated cyclohexenones **(*S,R*)-7**, **(*R,S*)-7** and **(*S,S*)-7** were obtained in an excellent combined yield of 95 % with a diastereomeric *cis*-*trans*-ratio of 1 : 1.9. Fortunately, the *cis*-product (*S,S*)-**7** was formed with an excellent enantiomeric excess (*ee*) of 97 % whereas the *trans*-isomer showed an *ee* of only 43 % (entry 3, Table 1).[18]

Having in hand the highly enantioenriched cyclohexenone **(*S,S*)-7** we set out to finish the synthesis. Fortunately, the addition of MeCu using previously established conditions provided good access to the anticipated cyclohexanone **8** which was subsequently reacted into the corresponding allylvinylcarbonate **9** With this compound in hand we investigated the stereochemical course of the second decarboxylative Tsuji-Trost allylation, however we were disappointed to see that the new C-C-bond was formed with high diastereoselectivity to product **10** with the undesired relative *trans*-configuration of two exocyclic carbonyl-groups (Scheme 1).



SCHEME 1. Diastereoselective synthesis of cyclohexanone **10**.

This diastereoselective course might be rationalized assuming that the pseudo-equatorial arrangement of both the allyl and isoprenyl side-chains in **9** hinders the addition of the allyl-Pd complex from the top face leading to the undesired product **10** (Figure 2). Looking at this model we anticipated that one of the axial-oriented methyl groups would be the only way to overcome this steric interaction if the two unsaturated side-chains would be tied together using a cross-metathesis within a bicyclo[4.3.1]undecenone in which the enolate is accessible from the top face (Figure 2).

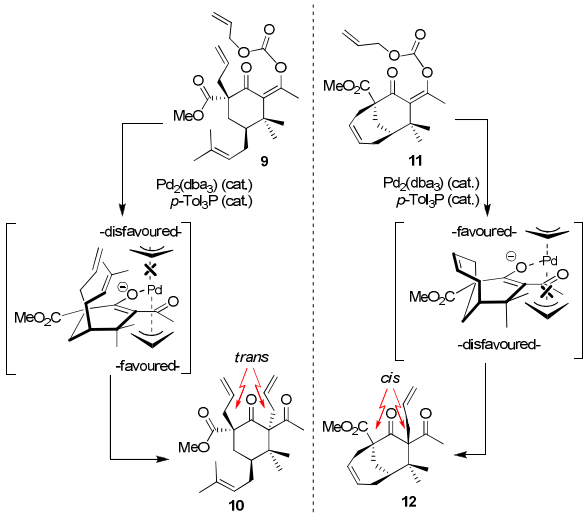
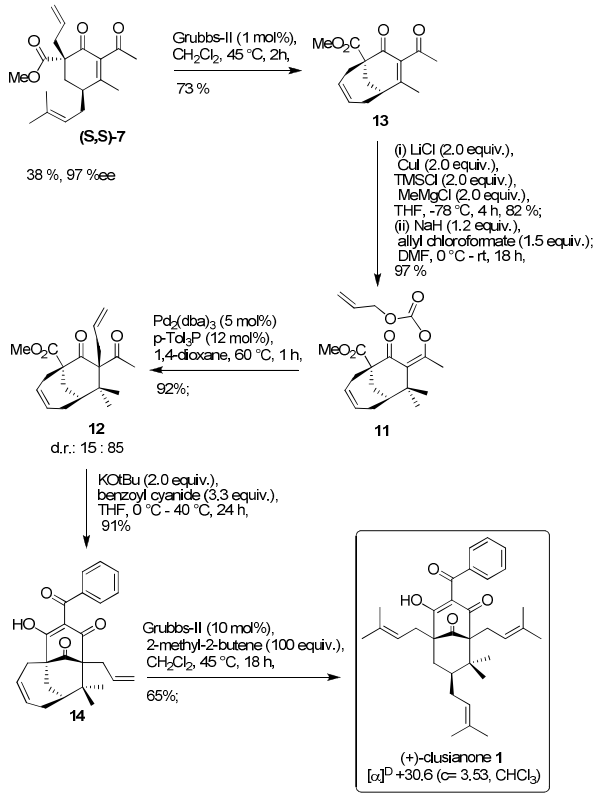


Figure 2. Directing the diastereoselective course of the final Tsuji-Trost allylation via RCM-ROCM.

Gratifyingly, treatment of **(*S,S*)-7** with Grubbs second generation metathesis catalyst provided the desired bicyclo[4.3.1]decenone core in **13** in excellent yield (Scheme 2). **13** was subjected to the 1,4-addition-alloc formation to give allylvinylcarbonate **11** in excellent yield as a single regioisomer.



SCHEME 3. The total synthesis of (+)-clusianone.

The subsequent Pd-catalyzed decarboxylative allylation gave product **12** as a mixture of two diastereomers in a ratio of 15:85 in favor of the desired diastereomer. Base mediated intramolecular Claisen-condensation-benzoylation led to the

View Article Online
DOI: 10.1039/C4CC09701G

formation of the tetracyclic intermediate **14** which reacted with iso-amylene in the presence of a Ru-carbene catalyst in a ROCM sequence to give the perprenylated natural product (Scheme 2). *In total we finished the enantioselective total synthesis of (+)-clusianone within 11 steps starting from acetylacetone in an overall yield of 8 %.* Spectroscopic data and optical rotation are in perfect agreement with the data reported in the literature. Moreover, we were able to assign the absolute configuration of (+)-clusianone through x-ray analysis of bicycle **13** (Figure 3).

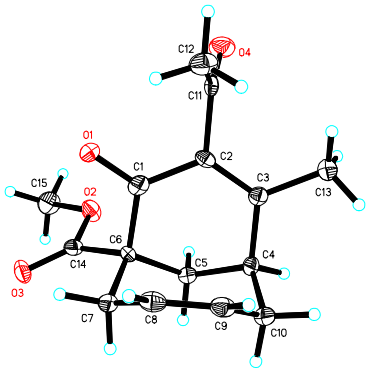


Figure 3. X-ray structure of enantiopure bicycle **13**

In summary we report here a short and concise enantioselective total synthesis of (+)-clusianone, a *cis*-(or *exo*-)type B PPAP with reported activities against HIV and Eppstein-Barr virus. An asymmetric Tsuji-Trost allylation, and a sequence of Ru-catalyzed ring closing metathesis plus subsequent diastereoselective Tsuji-Trost allylation represent the key steps within this synthetic route. The successful application of these methods on complex functional substrates not only underlines the advanced status of current organometallic catalysis, but it also enabled us to extend our PPAP-synthesis algorithm to the *exo*-type B PPAPs without alteration of the synthetic operations.

Notes and references

[a] *Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany; Tel: +49-711-68564283; E-mail: bernd.plietker@oc.uni-stuttgart.de*

† Electronic Supplementary Information (ESI) available: General procedure for the preparation of all new compounds including full characterization. See DOI: 10.1039/b000000x/

[1] R. Ciochina, R. B. Grossman, *Chem. Rev*., 2006, **106**, 3963.
[2] (a) J.-A. Richard, R. H. Pouwer, D. Y.-K. Chen, *Angew. Chem. Int. Ed.,* 2012, **51**, 4536. (b) J. T. Njardarson, *Tetrahedron*, 2011, **67**, 7631.
[3] (a) I. P Singh, S. B. Bharate, *Nat. Prod. Rep*., 2006, **23**, 558. (b) I. P. Singh, J. Sidana, S. B. Bharate, W. Foley, *Nat. Prod. Rep*., 2010, **27**, 393.
[4] J. H. George, M. D. Hesse, J. E. Baldwin, R. M. Adlington, *Org. Lett.,* 2010, **12**, 3532.
[5] (a) N. Biber, K. Möws, B. Plietker, *Nature Chem*., 2011, **3**, 938. (b) K. Lindermayr, B. Plietker, *Angew. Chem*. Int. Ed., 2013, **52**, 12183. (c) F. Horeischi, N. Biber, B. Plietker, *J. Am. Chem. Soc*., 2014, **136**, 4026. (d) Q. Zhang, J. A. Jr. Porco, *Org. Lett*., 2012, **14**, 1796. (e) Q. Zhang, B. Mitasev, J. Qi, J. A. Jr. Porco, *J. Am. Chem. Soc*., 2010, **132**, 14212.**[6]** (a) S. J. Spessard, B. M. Stoltz, *Org. Lett*., 2002, **4**, 1943. (b) T. Pouplin, B. Tolon, P. Nuhant, B. Delpech, C. Marazano, *Eur. J. Org. Chem*., **2007**, 5117. (c) G. Mehta, T. Dhanbal, M. K. Bera, *Tetrahedron Lett.,* 2010, **51**, 5302. (d) V Rodeschini, N. M Ahmad, N. S. Simpkins, *Org. Lett*., 2006, **8**, 5283. (e) N. M. Ahmad, V. Rodeschini, N. S. Simpkins, S. E. Ward, A. J. Blake, *J. Org. Chem.,* 2007, **72**, 4803. (f) P. Nuhant, M. David, T. Pouplin, B. Delpech, C. Marazano, *Org. Lett*., 2007, **9**, 287.
[7] (a) H. Usuda, M. Kanai, M. Shibasaki, *Org. Lett*. 2002, **4**, 859. (b) H. Usuda, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* 2002, **43**, 3621. (c) Y. Shimizu, A. Kuramochi, H. Usuda, M. Kanai, M. Shibasaki, *Tetrahedron Lett*. 2007, **48**, 4173. (d) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*., 2005, **127**, 14200.
[8] (a) C. Tsukano, D. R. Siegel, S. J. Danishefsky, *Angew. Chem. Int. Ed*., 2007, **46**, 8840. (b) D. R. Siegel, S. J.; Danishefsky, *J. Am. Chem. Soc.,* 2006, **128**, 1048.
[9] (a) J. Qi, J. A. Jr. Porco, *J. Am. Chem. Soc*., 2007, **129**, 12682. (b) B. Mitasev, J. A. Jr.; Porco, *Org. Lett.,* 2009, **11**, 2285. (c) M. Uwamori, M. Nakada, *Nat. Prod. Commun*., 2013, **8**, 955.
[10] G. Bellavance , L. Barriault, *Angew .Chem. Int. Ed.,* 2014, **53**, 6701.
[11] (a) M. R. Garnsey, D. Lim, J. M. Yost, D. M. Coltart, *Org. Lett*., 2010, **12**, 5234. (b) M. R. Garnsey, J. A. Matous, J. J. Kwiek, M. D. Coltart, *Bioorg. Med. Chem. Lett*., 2011, **21**, 2406.
[12] J. H. Boyce, J. A. Jr. Porco, *Angew. Chem. Int. Ed*., 2014, **53**, 7832.
[13] V. Rodeschini, N. S. Simpkins, C. Wilson, *J. Org. Chem*., 2007, **72**, 4265.
[14] (a) J. Qi, A. B. Beeler, Q. Zhang, J. A. Jr. Porco, *J. Am. Chem. Soc*., 2010, **132**, 13642. (b) Y. Shimizu, S. L. Shi, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.,* 2010, **49**, 1103. (c) B. A. Sparling, D. C. Moebius, M. D. Shair, *J. Am. Chem. Soc.,* 2013, **135**, 644.
[15] J. A. Keith, D. C. Behenna, N. Sherden, J. T. Mohr, S. Ma, S. C. Marinescu, R. J. Nielsen, J. Oxgaard, B. M. Stoltz, W. A. Goddard, *J. Am. Chem. Soc*., 2012, **134**, 19050.
[16] (a) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.,* 2009, **131**, 18343. (b) B. M. Trost, J Xu, *J. Am. Chem. Soc.,* 2005, **127**, 2846.
[17] (a) anti-HIV-activity: A. L. Piccinelli, O. Cuesta-Rubio, M. B. Chica, N. Mahmood, B. Pagano, M. Pavone, V. Barone, L. Rastelli, *Tetrahedron Lett.*, 2005, **61**, 8206. (b) anti-Epstein-Barr virus: C. Ito, M. Itoigawa, Y. Miyamoto, S. Onoda, K. S. Rao, T. Mukainaka, H. Tokuda, H. Nishino, H. Furukawa, *J. Nat. Prod.*, 2003, **66**, 206.**[18]** For a rationale for the stereoselective course of asymmetric Tsuji-Trost allylation see supportings part I.