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Development of a Strategy for the Asymmetric Synthesis of Polycyclic Polyprenylated Acylphloroglucinols via *N*-Amino Cyclic Carbamate Hydrazones: Application to the Total Synthesis of (+)-Clusianone

Michelle R. Garnsey, Daniel Lim, Julianne M. Yost, and Don M. Coltart*

Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

don.coltart@duke.edu

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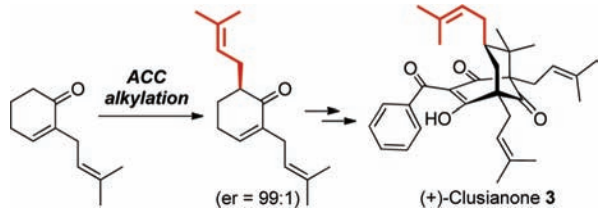
ABSTRACT



A broadly applicable asymmetric synthetic strategy utilizing *N*-amino cyclic carbamate alkylation that provides access to the various stereochemical permutations of a common structural motif found in many polycyclic polyprenylated acylphloroglucinols is described. The utility of this methodology is demonstrated through the first asymmetric total synthesis of the antiviral agent (+)-clusianone.

The polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large and remarkably interesting class of natural products.[1] Not only do these compounds exhibit wide-ranging biological activity but also they possess intriguing structures. Consequently, they have attracted considerable interest from the synthetic community, and a number of PPAPs have now been synthesized using a variety of innovative approaches.[2] Despite the impressive advances resulting from this work, only a small number of syntheses have been conducted in an asymmetric fashion.[2e,i,3] We recently described a new method for the asymmetric α-alkylation of ketones based on the use of chiral *N*-amino cyclic carbamate (ACC) auxiliaries.[4] In what follows, we outline a general asymmetric synthetic strategy utilizing this alkylation method that provides access to the various stereochemical permutations of a common structural motif found in many PPAPs. The synthetic potential of the resulting intermediates is highlighted by the first asymmetric total synthesis of the antiviral[5,6] agent (+)-clusianone (Scheme 1).

(1) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963–3986.

(2) (a) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048–1049. (b) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201. (c) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287–289. (d) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283–5285. (e) Rodeschini, V.; Simpkins, N. S.; Wilson, C. *J. Org. Chem.* **2007**, *72*, 4265–4267. (f) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803–4815. (g) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840–8844. (h) Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 12682–12683. (i) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103–1106.

(3) Simpkins has reported the synthesis of optically active (+)-clusianone, but this was achieved through chiral resolution of an advanced intermediate. See ref 2e.

(4) Lim, D.; Coltart, D. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5207–5210.

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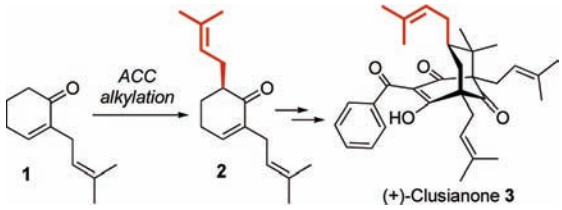
Scheme 1. Asymmetric Total Synthesis of (+)-Clusianone via Asymmetric ACC Alkylation



Presently, well over 100 PPAPs are known.[1] They are categorized as type A, B, and C, depending on the position of the benzoyl moiety (Figure 1a);[1,7] (+)-clusianone is a type

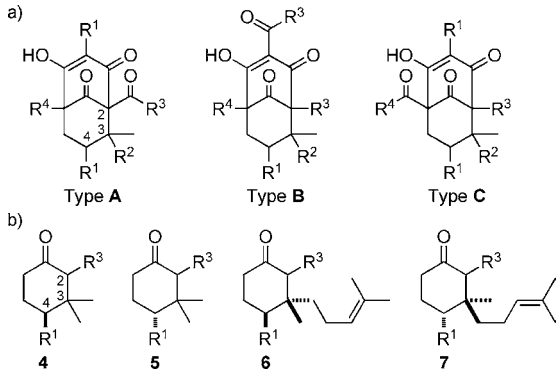
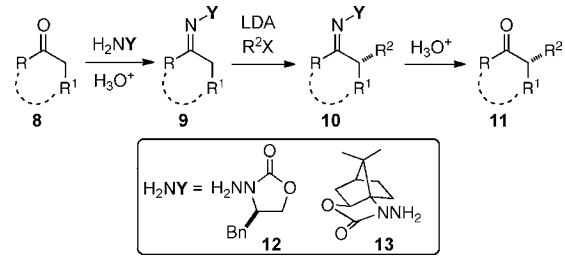


Figure 1. (a) Type A, B, and C PPAPs. (b) Naturally occurring stereochemical permutations of the C3- and C4-alkyl groups.

B system. The 2,3,3,4-tetrasubstituted cyclohexanone scaffold is a common structural motif that is shared by the majority of all known PPAPs.[1] In these systems, the 2- and 4-positions are always stereogenic, and the 3-position is either dimethylated or substituted with a methyl and a homoprenyl group and, therefore, also stereogenic. With regard to absolute configuration, the naturally occurring substitution patterns[1] are shown in Figure 1b. We reasoned that if a general asymmetric synthesis of the 2,3,3,4-tetrasubstituted cyclohexanone core was available that provided access to these naturally occurring stereochemical patterns then it could provide the basis for the asymmetric total synthesis of a substantial proportion of all PAPPs.

We recently described the use of chiral *N*-amino cyclic carbamate (ACC) auxiliaries for the asymmetric α-alkylation of ketones (Scheme 2).[4] ACC auxiliaries react readily with ketones to afford the corresponding hydrazones (**8** → **9**).

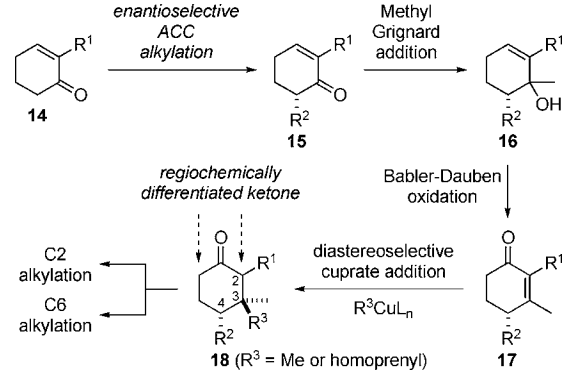
Scheme 2. Asymmetric Alkylation of Ketones via Chiral ACC Auxiliaries



These undergo rapid deprotonation to the azaenolates, which alkylate on up to a multigram scale with excellent stereoselectivity and yield (**9** → **10**). Moreover, the auxiliaries can be recovered quantitatively and recycled (**10** → **11** + H_2N**Y**). It occurred to us that this alkylation procedure could provide the basis for an efficient and general asymmetric approach to the desired 2,3,3,4-tetrasubstituted cyclohexanone core and thus open the door to the asymmetric total synthesis of a range of PPAPs.

The synthetic strategy that we envisioned is shown in Scheme 3. A 2-substituted cyclohexenone **14**[8] would serve

Scheme 3. Proposed General Strategy for the Asymmetric Synthesis of the PPAP Core Structure



as the substrate for enantioselective ACC alkylation, ultimately giving enone **15**. Grignard addition would then be used to install the C3 methyl group (**15** → **16**), which would be followed by a Babler−Dauben oxidation[9] producing transposed enone **17**. At this point, the cyclohexenone would undergo either methyl cuprate addition to produce the C3 *gem*-dimethyl moiety or diastereoselective 1,4-addition[10] using a homoprenyl cuprate to secure the C3 stereocenter (**17** → **18**).

(5) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206–8211.

(6) Ito, C.; Itoigawa, M.; Miyamoto, Y.; Onoda, S.; Sundar Rao, K.; Mukainaka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2003**, *66*, 206–209.

(7) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279–283.

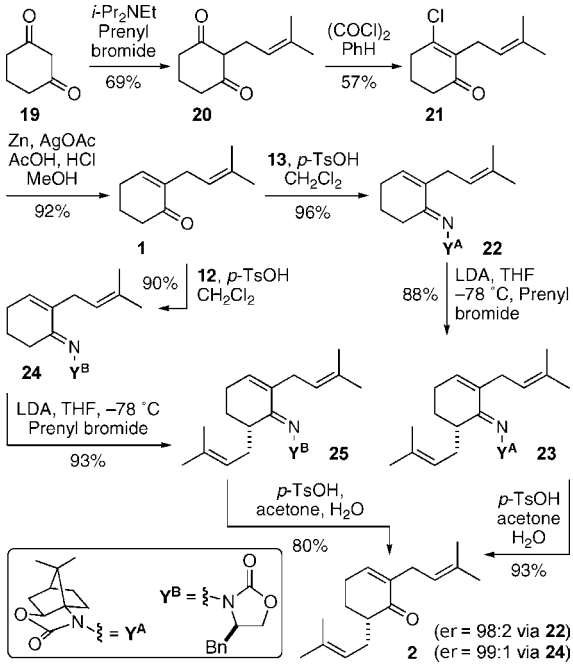
(8) For representative synthetic approaches to such compounds, see: (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636–643. (b) Taber, D. F. *J. Org. Chem.* **1976**, *41*, 2649–2650.

(9) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469–474. Dauben, W. G.; Michno, D. M. *J. Am. Chem. Soc.* **1977**, *42*, 682–685.

(10) Breit, B.; Dremel, P. Copper-mediated Diastereoselective Conjugate Addition and Allylic Substitution Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 188−223.

We began our studies by preparing enone **1** using a combination of literature procedures (Scheme 4).[2c,8a] Thus, 1,3-

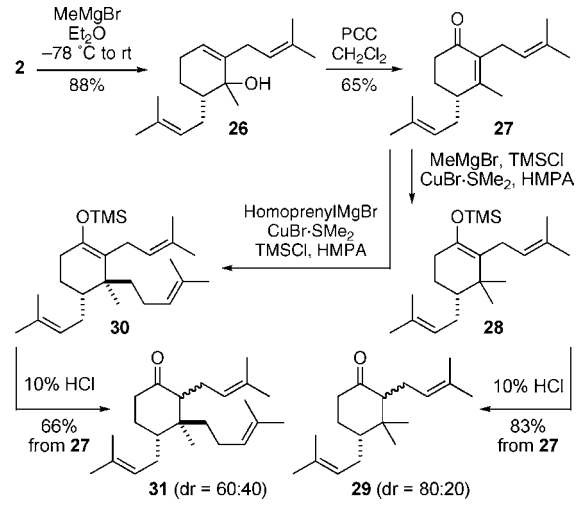
Scheme 4. Asymmetric Synthesis of Advanced Ketone Intermediate **2** by Using Enantioselective ACC Alkylation



cyclohexadione (**19**) was prenylated, and the product was subsequently treated with oxalyl chloride to generate β-chloro enone **21**. Metallic reduction (**21** → **1**) gave the desired enone substrate for the ACC alkylation sequence.[4] On the basis of our previous success with auxiliary **13** in various alkylations,[4] hydrazone **22** was prepared. It was then alkylated in excellent yield by treatment with LDA and prenyl bromide (**22** → **23**). The auxiliary was removed from the alkylated product (**23** → **2**) by treatment with *p*-TsOH·H_2O in acetone/H_2O, which gave the desired ketone with excellent overall asymmetric induction (er = 98:2).[11,12] The (*S*)-configuration at the new stereogenic center was inferred by analogy to our previous studies.[4] With ketone **1** in hand, we also tested the alkylation using the phenylalanine-based auxiliary **12**. To our surprise, unlike our previous experience with acyclic ketones,[4] the enantioselectivity (er = 99:1)[11,12] of the alkylation was even better in this case than it was when auxiliary **13** was used.[13] The stereochemical outcome of this reaction was deduced by comparison to the methylation of the corresponding 2-methylcyclohexenone-derived ACC hydrazone, for which a crystal structure of the product was obtained.[14]

With a reliable route to advanced ketone **2** secured, we initiated the proposed methylation/carbonyl transposition sequence. To do this, **2** was treated with MeMgBr, forming tertiary allylic alcohol **26** as a mixture of diastereomers (Scheme 5). These were used without separation in a Babler–Dauben

Scheme 5. Synthesis of Representative PPAP Core Structures



oxidation[9] to produce enone **27**. Compound **27** is common to the preparation of the different PPAP motifs shown in Figure 1 and marks a divergence point in the synthetic strategy. As such, to access the *gem*-dimethyl function (cf. **5**), the Simpkins conjugate addition protocol[2d] was employed, which provided smooth access to **28**. Silyl enol ether **28** could be readily hydrolyzed to give ketone **29** as a mixture of diastereomers. Separately, the β-homoprenyl substituent was installed in an analogous fashion using a homoprenyl Grignard reagent.[15] We were pleased to find that this transformation proceeded with excellent diastereoselectivity, with **30** being the only conjugate addition product detected.[16] In this case, however, the silyl enol ether function was not sufficiently stable to silica gel[17] chromatography to give a high yield of pure **30**, so we chose to hydrolyze it directly to ketones **31**. The relative configuration between the C3 and C4 substituents was confirmed by X-ray crystallography of the *p*-tolyl-*N*-sulfonyl hydrazone derivative of the 2-β diastereomer of **31**.[14]

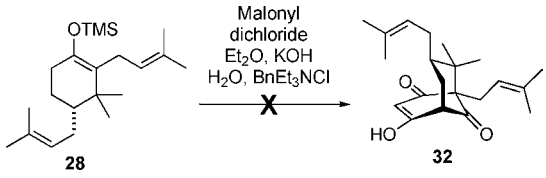
Satisfied that we had established a suitably general approach to the key PPAP motifs identified above (see Figure 1), we undertook the extension of this strategy to the first asymmetric total synthesis of (+)-clusianone.[3] (+)-Clusianone has been shown to possess antiviral activity against both HIV (EC_{50} = 0.020 ± 0.003 μM)[5] and Epstein–Barr virus (17.4 ± 1.2% of cells were EBV-EA positive in the presence of 32 nmol of **3**).[6] As such, it is a compelling target for further biological investigation as an antiviral agent.

Our initial approach to (+)-clusianone utilized silyl enol ether **28**. Inspired by work from the Stoltz laboratory,[18] we intended

(11) Major enantiomer shown.
(12) Established using chiral HPLC by reference to independently prepared racemic material. See the Supporting Information for details.
(13) Investigations into the origins of this differential selectivity are underway.
(14) See the Supporting Information for details.
(15) Ohloff, G.; Giersch, W.; Decorzant, R.; Buechi, G. *Helv. Chim. Acta* **1980**, *63*, 1589–1597.
(16) Small amounts (<10%) of the 1,2-addition products were also produced.
(17) Pre-treated with 1:1:98 Et_3N–EtOAc–hexanes.

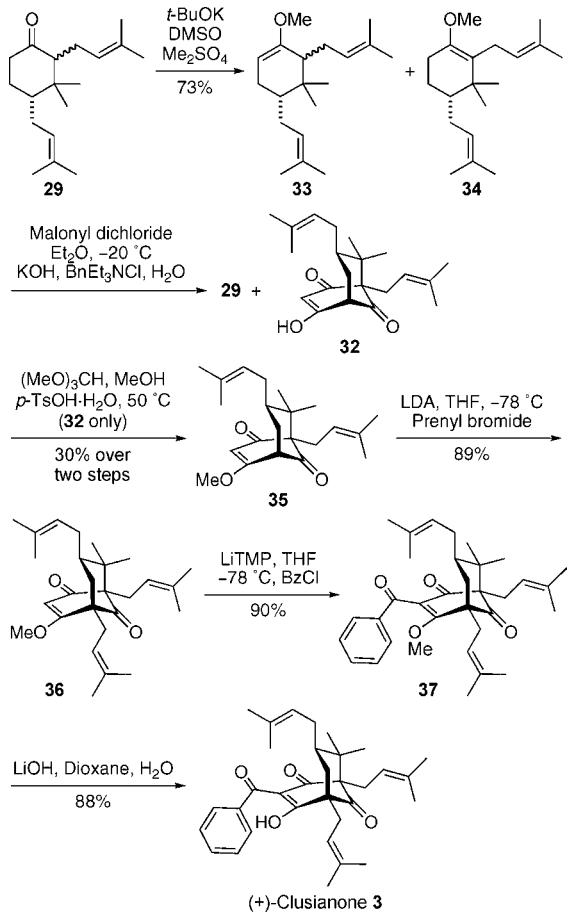
to engage **28** in an Effenberger cyclization[19] to access the bicyclic framework of **32** diastereoselectively (Scheme 6).

Scheme 6. Initial Attempt at the Synthesis of Advanced Bicyclic Intermediate **32**



Unfortunately, our attempts to effect this transformation were uniformly unsuccessful. We therefore utilized an alternative strategy for the remaining transformations developed by Simpkins in his synthesis of racemic clusianone,[2d] which instead employed methyl enol ethers **33** and **34** for the Effenberger cyclization. The enol ethers were readily prepared as outlined in Scheme 7 and indeed underwent the intended cyclization.

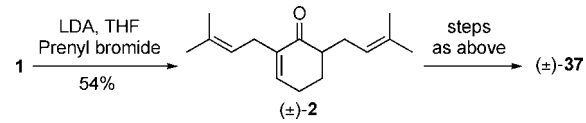
Scheme 7. Asymmetric Total Synthesis of (+)-Clusianone (**3**)



Careful acid/base extraction was required to separate the desired product (**32**) from **29**, and the latter was able to be recycled to produce more of **33** and **34**. Methylation of crude cyclized product **32** gave **35** in 30% yield over the two steps (71% based on recovered **29**). Next, **35** was subjected to bridgehead prenylation, which gave **36** in excellent yield. Subsequent addition of the benzoyl group (**36** → **37**), followed by methyl enol ether hydrolysis (**37** → **3**), gave (+)-clusianone.

To determine the enantiomeric purity of our synthetic material, the above synthetic sequence was carried out in a racemic fashion to the stage of the penultimate compound. Thus, enone **1** was subjected to LDA-mediated prenylation, producing (±)-**2** (Scheme 8). This compound was then subjected to the transformations developed above to give (±)-**37**. Conditions

Scheme 8. Synthesis of (±)-**37**



were then established that gave baseline resolution of the enantiomers of (±)-**37** by chiral HPLC. Subsequent analysis of our synthetic **37** revealed an er = 99:1.[14]

In conclusion, we have developed an effective synthetic strategy that provides access to the 2,3,3,4-tetrasubstituted cyclohexanone scaffold, a common structural motif that is shared by the majority of the over 100 known PPAPs. A key transformation of this synthetic sequence is a highly enantioselective (er = 99:1) ketone α-alkylation sequence, which is achieved using our recently developed ACC alkylation method.[4] Subsequent methylation and carbonyl transposition produces the key advanced intermediate **27**, for either methylation or diastereoselective homoprenylation, thus securing the 2,3,3,4-tetrasubstituted cyclohexanone core. To demonstrate the utility of this strategy for the synthesis of PPAPs, the first asymmetric total synthesis of (+)-clusianone[3] was conducted, taking advantage of late-stage transformations developed by Simpkins in his racemic clusianone.[2d] Further investigations are underway on the asymmetric total synthesis of other PPAPs using this general strategy.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds, as well as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943–1946.
(19) Schonwalder, K. H.; Kollat, P.; Stezowski, J. J.; Effenberger, F. *Chem. Ber.* **1984**, *117*, 3280–3296.