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Pauson−Khand Adducts of *N*-Boc-propargylamine: A New Approach to 4,5-Disubstituted Cyclopentenones

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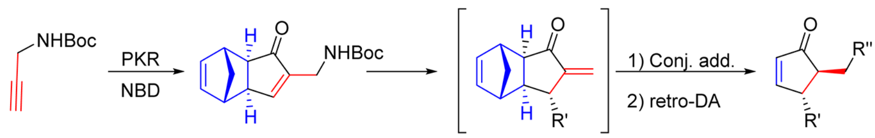
ABSTRACT



A new approach to the synthesis of 4,5-disubstituted cyclopentenones is described. The strategy is based on the Pauson−Khand (PK) reaction of norbornadiene and N-Boc-propargylamine as an alkyne with a masked leaving group, which can be eliminated at will. This approach to the synthesis of 4,5-disubstituted cyclopentenones overcomes the problem of using the alkylation to introduce the α side chain. As an example, prostane 13-*epi*-12-oxo-phytodienoic acid (13-*epi*-12-oxo-PDA) methyl ester was synthesized.

Cyclopentanic compounds are abundant in nature and exhibit a wide range of structures and biological functions. Among them, prostanes are one of the largest biologically relevant classes of compounds.[1] They are generated as a product of the action of cyclooxygenases (COX) on fatty acids from the phospholipid bilayer. The most common substrate for this reaction cascade in the human body is arachidonic acid, which gives rise to prostaglandins.[2] A similar process occurs in plants, but linolenic acid is the main substrate and the corresponding prostanes are called phytoprostanes.[2a,3] Most share a disubstituted cyclopentane ring with different degrees of oxidation as the principal structural subunit. The 4,5-disubstituted cyclopentenone fragment is present in prostanes A and J as in the examples shown in Figure 1.

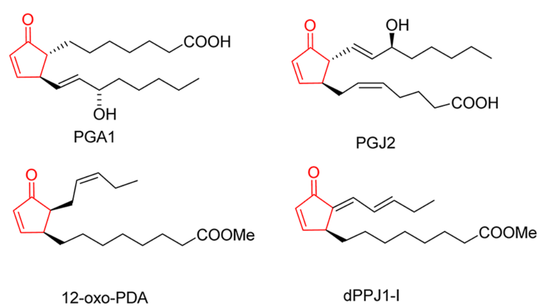


Figure 1. Biologically relevant 4,5-disubstituted cyclopentenones.

A convenient strategy to synthesize complex cyclopentenones consists of uncovering the enone functionality at the last step through a retro-Diels−Alder (r-DA) reaction. Grieco pioneered this method using dicyclopentadiene derivatives (with *endo*-stereochemistry) as starting materials.[4] The intermolecular Pauson−Khand reaction (PKR) (a cobalt-catalyzed cycloaddition between an alkyne, an alkene, and CO to give a cyclopentenone) is particularly suited for the preparation of similar compounds, although with *exo* stereochemistry.[5,6] The norbornene fragment of these PK adducts can be considered as a masked enone that also plays a fundamental stereodirecting role on the

[†] Institute for Research in Biomedicine (IRB Barcelona).
[‡] Universitat de Barcelona.
(1) Marks, F.; Fürstenberg, G. *Prostaglandins, Leukotrienes and other Eicosanoids*; Wiley-VCH: Weinheim, 1999.
(2) (a) Jahn, U.; Galano, J. M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894. (b) Saibal, D.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286.
(3) (a) Sembdner, G.; Parthier, B. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1993**, *44*, 569. (b) Hamberg, M.; Gardner, H. W. *Biochim. Biophys. Acta* **1992**, *1165*, 1.
(4) (a) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008. (b) Grieco, P. A.; Abood, N. *J. Chem. Soc., Chem. Commun.* **1990**, 410.

10.1021/ol400999a

Scheme 1. Retrosynthetic Analysis of 4,5-Disubstituted Cyclopentenones via PKR

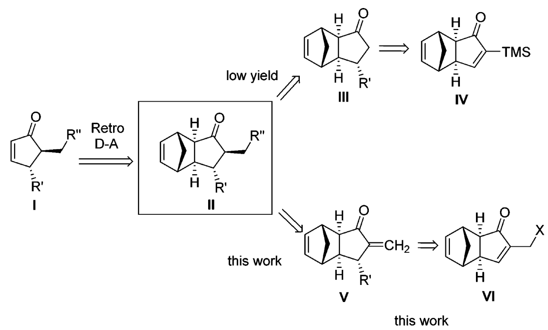
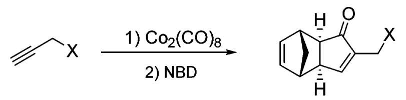


Table 1. PKR of Norbornadiene with Alkynes **1**



1a-e **2a-e**

entry	X	PK conditions	product	yield
1	SPh	toluene, 60 °C, 4 h	**2a**	40%
2	OPh	toluene, 70 °C, 4 h	**2b**	71%
3	NMe_2	hexanes, 60 °C, 3 h	**2c**	87%
4	NMeBoc	toluene, 65 °C, 24 h	**2d**	85%
5	NHBoc	hexanes, 60 °C, 3 h	**2e**	61%

conjugate additions to the cycloadducts. The PKR of norbornadiene (NBD) with a large variety of alkynes provides tricyclic compounds, which, after chemical modifications, can experience r-DA reactions to afford the desired cyclopentenones. The known asymmetric versions of the intermolecular PKR[7] add value to this approach, which has been applied to the enantioselective total synthesis of Brefeldin A,[8] the carbanucleosides Avacavir and Carbovir,[9] and prostanes $dPPJ_1$ (I and II).[10] Although the synthesis of chiral 4-substituted cyclopentenones or 5-alkylidenecyclopen-2-enones starting from the PK adduct of NBD and trimethylsilylacetylene (**IV**) was successful,[9,10] the introduction of a saturated α side chain to the carbonyl (from **III** to **II**) was troublesome (Scheme 1). Although the conjugate addition/desilylation to give **III** works well,[11] the alkylation of these compounds produces mixtures of starting material and alkylated and dialkylated products.[12] To overcome this problem, we planned the synthesis of the exocyclic enones **V**, which could undergo a second conjugate addition, thus giving the desired precursors **II**. We envisaged the preparation of enones **V** from PK adducts **VI** with a potential leaving group X. Here we describe the synthesis of 4,5-disubstituted cyclopentenones via conjugate addition of *exo*-methylene cyclopentenones followed by r-DA. For this purpose, we developed a practical sequence for the asymmetric synthesis of these exocyclic enones via PK reaction of *N*-Boc-propargyl amines. We also describe the application of our method to the enantioselective synthesis of 13-*epi*-12-oxo-phytodienoic acid (13-*epi*-12-oxo-PDA) methyl ester.

We first chose phenyl propargyl thioether **1a** as an alkyne with a potential leaving group, since we considered that sulfide oxidation could facilitate elimination. Phenyl propargyl ether **1b** was also selected, since it could lead to the exocyclic enone by acidic treatment. Finally, we chose *N,N*-dimethyl, *N*-methyl-*N*-Boc, and *N*-Boc propargyl amine derivatives **1c**–**e**, because the elimination could be promoted by alkylation. The PK reaction of all of these alkynes **1a**–**e** with NBD under thermal conditions took place uneventfully, affording tricyclic cyclopentenones **2a**–**e** in satisfactory yields (Table 1).

With the PK adducts **2a**–**e** in hand, we studied conjugate additions to this enones, using lithium dibutyl cuprate as the initial convenient reagent. Unexpectedly, treatment of adduct **2a** bearing a thioether function with the cuprate at low temperature afforded the double addition product **3a**. Most probably, once the first conjugate addition is performed, the enolate intermediate evolves rapidly, even at low temperature, giving rise to the exocyclic enone. This enone would react *in situ* in a 1,4 addition manner with an excess of reagent, thus providing **3a** and diphenyldisulfide (Table 2, entry 1). Propargyl alcohol derivative **2b** and dimethylpropargylamine **2c** behaved similarly to **2a**, providing the double addition product **3a** (Table 2 entries 2, 3). This unexpected result led us to address carbamate derivatives. Gratifyingly, neither the *N*-methyl-*N*-Boc-propargylamine **2d** nor *N*-Boc-propargylamine **2e** experienced the *in situ* elimination and afforded the expected conjugate addition products **4** and **5** respectively (Table 2, entries 7, 8). Therefore, only adducts containing a Boc-protected amine did not undergo the process of double conjugate addition previously described. To test the generality of these two processes, we studied different reaction conditions on theses substrates. As before, compounds **2a**–**c** gave double addition of nitromethane (entries 4–6) whereas Boc-protected propargylamine **2e** afforded the 1,4-addition product **5b** (Table 2, entry 9). Although disubstituted products **3** are not suitable for our present synthetic objectives, this tandem conjugate addition/elimination/conjugate addition in one pot was remarkable and is currently being studied in more

(5) For recent reviews on the Pauson–Khand reaction, see: (a) Lee, H.; Kwong, F. *Eur. J. Org. Chem.* **2010**, 789. (b) Park, J. H.; Chang, K.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461. (c) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32.

(6) *The Pauson-Khand Reaction*; Ríos, R.; WILEY-VCH: Weinheim, 2012.

(7) (a) Sola, J.; Reves, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020. (b) Ji, Y.; Riera, A.; Verdaguer, X. *Org. Lett.* **2009**, *11*, 4346. (c) Reves, M.; Achard, T.; Sola, J.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2008**, *73*, 7080. (d) Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *J. Am. Chem. Soc.* **2000**, *122*, 10242.

(8) Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670.

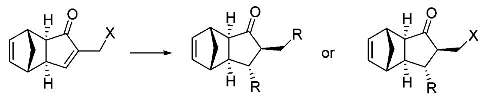
(9) Vazquez-Romero, A.; Rodriguez, J.; Lledó, A.; Verdaguer, X.; Riera, A. *Org. Lett.* **2008**, *10*, 4509.

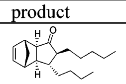
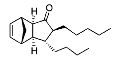
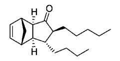
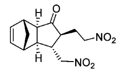
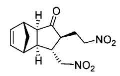
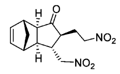
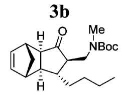
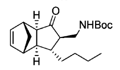
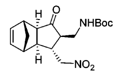
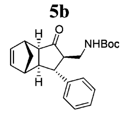
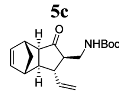
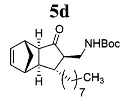
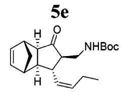
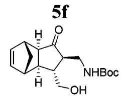
(10) (a) Iqbal, M.; Evans, P.; Lledó, A.; Verdaguer, X.; Pericàs, M. A.; Riera, A.; Loeffler, C.; Sinha, A. K.; Mueller, M. J. *ChemBioChem.* **2005**, *6*, 276. (b) Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledo, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem.* **2008**, *6*, 4649.

(11) Verdaguer, X.; Lledo, A.; Lopez-Mosquera, C.; Maestro, M. A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 8053.

(12) Lledó, A. PhD thesis, University of Barcelona, 2006.

Table 2. Conjugate Additions on PK Adducts **2**



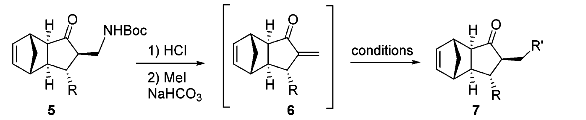
entry	sm	X	conditions	product	yield
1	**2a**	SPh	Bu_2CuLi	 **3a**	49%
2	**2b**	OPh	Bu_2CuLi	 **3a**	56%
3	**2c**	NMe_2	Bu_2CuLi	 **3a**	40%
4	**2a**	SPh	CH_3NO_2 TBAF	 **3b**	86%
5	**2b**	OPh	CH_3NO_2 TBAF	 **3b**	99%
6	**2c**	NMe_2	CH_3NO_2	 **3b**	46%
7	**2d**	NMeBoc	Bu_2CuLi	 **4a**	89%
8	**2e**	NHBoc	Bu_2CuLi	 **5a**	71%
9	**2e**	NHBoc	CH_3NO_2 TBAF	 **5b**	99%
10	**2e**	NHBoc	MgPhBr, CuI	 **5c**	77%
11	**2e**	NHBoc	CH_2CH-MgBr CuI	 **5d**	20%[a]
12	**2e**	NHBoc	$C_8H_{17}MgBr$ CuI	 **5e**	74%
13	**2e**	NHBoc	EtLi, CuI then acetylene	 **5f**	86%
14	**2e**	NHBoc	MeOH benzophenone hυ=254nm	 **5g**	73%

[a] Low yield due to the volatility of the product.

detail by our group. For our purposes, the PK adduct of Boc-propargylamine **2e** was selected as the most convenient substrate since the asymmetric PK reaction on this alkyne had already been studied.[13] A series of conjugate addition reactions on compound **2e** were subsequently

(13) Reves, M.; Lledó, A.; Ji, Y.; Blasi, E.; Riera, A.; Verdaguer, X. *Org. Lett.* **2012**, *14*, 3534.

Table 3. Elimination and Conjugate Addition of Compounds **5**



ent.	sm	R	conditions	prod.	R′	yield
1	**5a**	Bu	CH_2=CH-MgBr, CuI	**7ad**	vinyl	30%[a]
2	**5a**	Bu	CH_3NO_2 TBAF	**7ab**	CH_2NO_2	82%
3	**5d**	vinyl	Bu_2CuLi	**7db**	Bu	25%[a]

[a] Low yield due to the volatility of the product.

performed using a variety of reaction conditions (lithium dialkyl cuprates, Grignard reagents with copper(I) catalysis, nonorganometallic reagents, and photochemically activated reactions), affording compounds **5a**−**g** (Table 2, entries 8−14) in moderate to excellent yields.

Once we had prevented the spontaneous elimination of the potential leaving group in the reaction media, we next studied a procedure to promote this process at will in order to add a different fragment through a second conjugate addition. Acidic deprotection of the carbamate in compounds **5**, followed by treatment with $CH_3I/NaHCO_3$, afforded the desired exocyclic enones **6**. Due to the relative instability of these enones, which dimerized slowly, they were immediately subjected to a second conjugate addition, affording compounds **7** in moderate to good yields (Table 3). T3

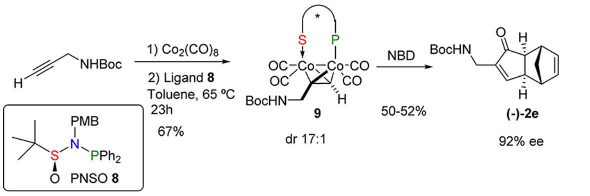
Once the method had been stablished in racemic form, an enantioselective version was pursued. PNSO ligands have been used in the PKR of *N*-Boc-propargylamine **1e** with tetramethylnorbornadiene.[13] PNSO ligand **8** gave excellent diastereoselectivities (up to 17:1) during the formation of cobalt complex **9**. The major diastereomer was purified by crystallization. Diastereomerically pure cobalt complex **9** was subjected to a PK reaction with NBD under either thermal or *N*-oxide-promoted conditions, yielding the enantiomerically enriched adduct **2e** in 87 to 92% ee, depending on the purity of the dicobalt complex used (Scheme 2). S2

To test our approach to the preparation of 4,5-disubstituted cyclopentenones, we applied it to the enantioselective synthesis of 13-*epi*-12-oxo-PDA methyl ester. 12-Oxo-phytodienoic acid (12-oxo-PDA) is a biosynthetic precursor of jasmonic acid via the allene oxide synthase pathway.[14] Jasmonic acid is formed during events of cellular stress and is thought to regulate aspects of fruit ripening, the production of viable pollen, and plant resistance to pathogens and insects, among other features. Several syntheses of *epi*-jasmonic acid have been developed,[15] but only a few processes have been described to lead to 12-oxo-PDA and its more stable epimer 13-*epi*-12-oxo-PDA.[4a,16]

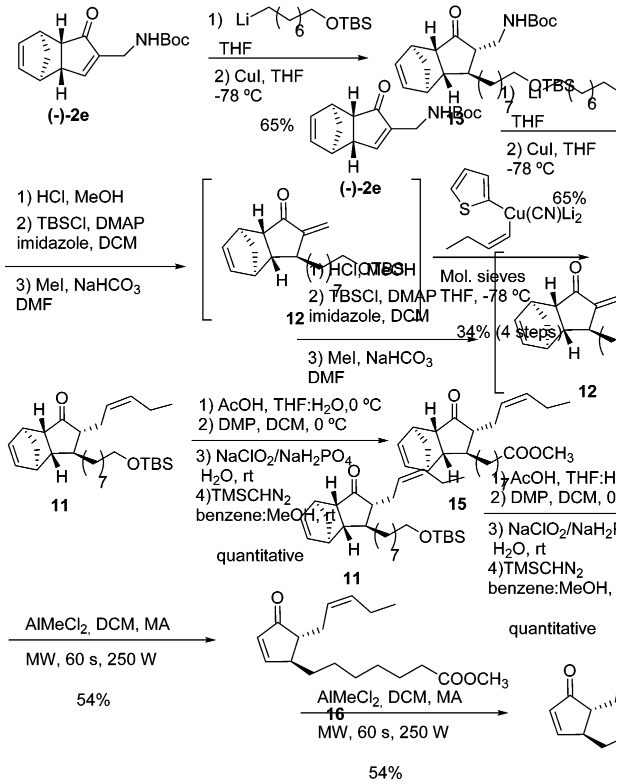
Our synthesis started from enantiomerically enriched PK adduct **(−)-2e**, which was treated with the cuprate reagent derived from 8-iodo-1-*tert*-butyldimethylsilyloxyoctane

(14) (a) Grechkin, A. N.; Mukhtarova, L. S.; Hamberg, M. *Biochem. J.* **2000**, *352*, 501. (b) Creelman, R. A.; Mullet, J. E. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1997**, *48*, 355.

Scheme 2. Enantioselective Version of PKR of *N*-Boc-propargylamine



Scheme 3. Enantioselective Synthesis of 13-*epi*-12-oxo PDA



(^{t}BuLi, CuI), to afford cyclopentanone **13** in 65% yield (Scheme 3). The *tert*-butyl carbamate in **13** was then deprotected with HCl/MeOH. Since the Boc group could not be selectively deprotected over the TBS group, both the amine and alcohol were reprotected[17] with TBSCl/Imidazole/DMAP. The resulting product was treated with MeI/$NaHCO_3$ in DMF without prior purification to afford the exocyclic enone **12**. The crude product of **12** was also used without previous purification. The cuprate reagent required for the conjugate addition of a *Z*-1-butenyl fragment was difficult to prepare. In 1979, Alexakis et al. reported the preparation of lithium di-(*Z*-butenyl) cuprate from ethyl lithium, copper iodide, and acetylene.[18] However, in our hands this methodology was difficult to reproduce due to the difficulty in measuring the amount of acetylene. Therefore, we opted to explore alternative, more robust, methodologies. We envisaged *Z*-1-bromobut-1-ene as the ideal precursor of *cis*-butenyl lithium cuprate since the corresponding bromide is readily accessible using Brevet's methodology.[19] Metalation of the bromide at low temperature with *tert*-BuLi, followed by addition to a suspension of usual copper salts (CuI, CuBr, CuBr·SMe_2), gave, in all cases, insoluble and unreactive reagents. Since our attempts to form the lithium di-(*Z*-butenyl) cuprate failed, a higher order cupprate[20] was tested. The reagent prepared from lithium 2-thienylcyanocuprate and (*Z*)-but-1-en-1-yl lithium allowed the reliable preparation adduct **11** in a remakable 34% overall yield over four steps. The silyl ether in **11** was further transformed into the corresponding methyl ester **15** by standard transformations in nearly quantitative yield. Final r-DA under Grieco's conditions[6] (maleic anhydride and $MeAlCl_2$ in anhydrous DCM) using microwaves afforded the desired product. We achieved an overall yield of 12% over 10 synthetic steps.

(15) (a) Roth, G. J.; Kirschbaum, S.; Bestmann, H. J. *Synlett* **1997**, 618. (b) Stadtmüller, H.; Knochel, P. *Synlett* **1995**, 463. (c) Kitahara, T.; Nishi, T.; Mori, K. *Tetrahedron* **1991**, *47*, 6999.
(16) (a) Ernst, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4054. (b) Kobayashi, Y.; Matsuumi, M. *Tetrahedron Lett.* **2002**, *43*, 4361. (c) Ainai, T.; Matsuumi, M.; Kobayashi, Y. *J. Org. Chem.* **2003**, *68*, 7825. (d) Nonaka, H.; Ogawa, N.; Maeda, N.; Wang, Y. G.; Kobayashi, Y. *Org. Biomol. Chem.* **2010**, *8*, 5212.
(17) Pratt, J. R.; Massey, F. H.; Pinkerton, F. H.; Thames, S. F. *J. Org. Chem.* **1975**, *40*, 1090.
(18) Alexakis, A.; Cahiez, G.; Normant, J. F. *J. Organomet. Chem.* **1979**, *177*, 293.
(19) Mori, K.; Brevet, J. L. *Synthesis* **1991**, *12*, 1125.
(20) Lipshutz, B. H.; Sengupta, S. *Organic Reactions*, Vol. 41; Paquette, L. A., Ed.; John Wiley and Sons, Inc.: New York, 1992.

In summary, here we described a new approach to 4,5-disubstituted cyclopentenones *via* an intermolecular PKR. We have solved the problem of the introduction of the α side chain by using an alkyne with a masked leaving group. This approach allowed the formation of a methylene cyclopentanone on which to perform a second conjugate addition. Thus, the PK adduct of NBD and *N*-Boc-propargylamine (also available in optically active form) was found to be a suitable product for our purposes. We performed a series of conjugate additions of distinct nucleophiles on the PK adduct. The removal of the Boc group followed by per-methylation afforded the exocylic enone which could be further functionalized by conjugate addition. The synthetic potential of this approach is reflected by the enantioselective synthesis of 13-*epi*-12-oxo-PDA.

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Supporting Information Available. Experimental procedures and characterization of all new compounds is available, along with ^{1}H and ^{13}C NMR spectra of products **2**, **3**, **4**, **5**, **7**, and all the intermediates for the synthesis of 13-*epi*-12-oxo PDA. This material is available free of charge via the Internet http://pubs.acs.org.

The authors declare no competing financial interest.