

Tetramethylnorbornadiene, a Versatile Alkene for Cyclopentenone Synthesis through Intermolecular Pauson–Khand Reactions

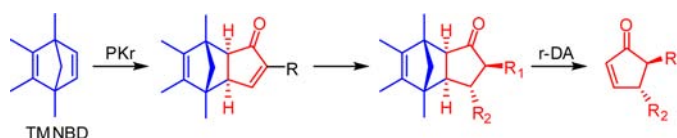
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ABSTRACT



1,2,3,4-Tetramethyl-bicyclo[2.2.1]hepta-2,5-diene (TMNBD, for *tetramethylnorbornadiene*) has been prepared and used successfully as an acetylene equivalent in the synthesis of substituted cyclopentenones. TMNBD is easily accessible on a multigram scale and displays excellent reactivity toward the intermolecular Pauson–Khand reaction. Conjugate additions on the resulting tricyclic compounds proceed with exquisite diastereoselectivity. The retro-Diels–Alder reaction of these TMNBD derivatives occurs under much smoother conditions than those required for its norbornadiene homologues.

Metal-mediated reactions play an important role in our continuing efforts toward new ways of constructing complex molecules. For the synthesis of five-membered rings, there is no match for the Pauson–Khand reaction (PKr) in terms of potential flexibility and atom economy.¹ This reaction, discovered in 1971 by Pauson and Khand,² is a transition-metal-mediated reaction with three components, an alkyne, an alkene, and carbon monoxide, which leads to variety of synthetically useful cyclopentenones.

A versatile application of norbornadiene Pauson–Khand adducts is the conjugate addition/retro-Diels–Alder sequence (Scheme 1).

The steric hindrance imposed by the norbornene ring enforces a diastereoselective addition from the *exo* face of

the cyclopentenone. After the corresponding *retro*-Diels–Alder (rDA) reaction, these products lead to cyclopentenone rings with different substituents and a defined stereochemistry.³

Such retro-Diels–Alder reactions have found wide application in synthesis.⁴ They can be performed under flash vacuum pyrolysis at high temperatures (500–600 °C) provided that the substrates are simple and robust enough.⁵ Alternative protocols at lower temperatures require the

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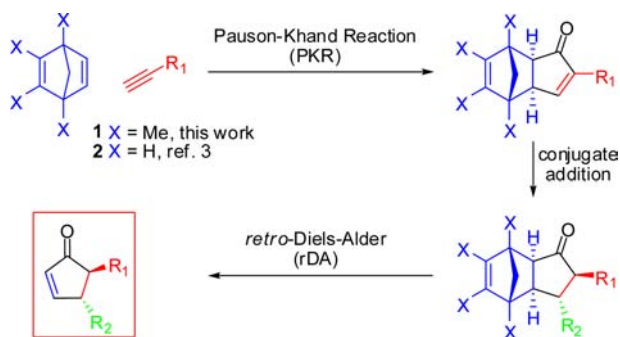
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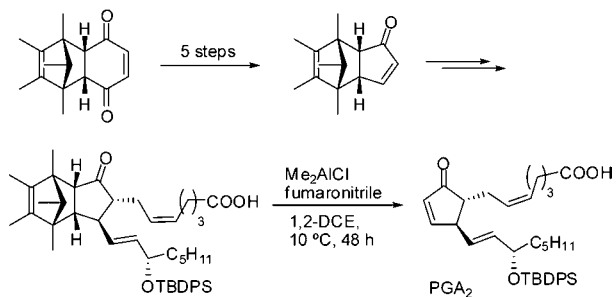
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Scheme 1. PKr–Conjugate Addition–rDA Sequence



presence of a Lewis⁶ or Brønsted⁷ acid and a diene scavenger. Under such conditions, however, the [4 + 2] cyclization of functionalized precursors suffers from accompanying side reactions (eliminations, isomerizations, etc.) which have hindered the use of this approach at late stages of elaborated syntheses. In the context of the synthesis of (+)-prostaglandin A₂, Grieco and Abood reported that cycloreversion could be accelerated by employing the corresponding pentamethyltricyclodecenones. These are derived in turn from the Diels–Alder adduct of pentamethylcyclopentadiene and benzoquinone (Scheme 2).⁸ Other substituted cyclopentadienes have also been employed as the leaving group with little relevance in synthetic terms.⁹

Scheme 2. Grieco's Strategy towards PGA₂^a



^aThe retro-Diels–Alder reaction was facilitated by the methyl groups.

We report here on the implementation of this strategy into our PKr-based approach to substituted cyclopentadienes. This route offers several advantages: a more favorable step count, the versatility of the PKr assembly toward the alkyne counterpart, and the stereodirecting ability of the

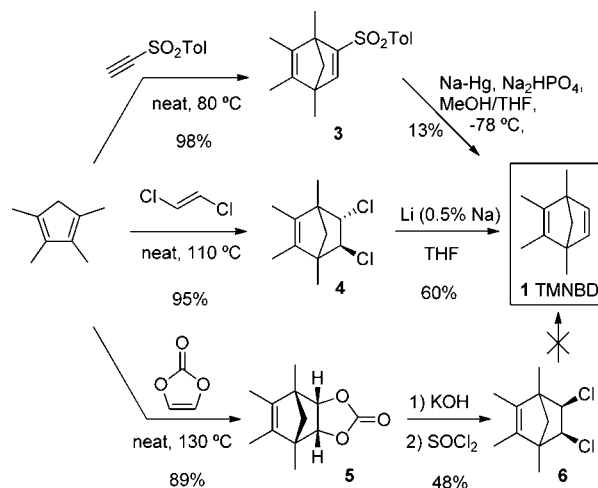
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exo-tricyclo[5.2.1.0^{2,6}]tricyclodeca-4,8-dien-3-one scaffold. Considering the success achieved with pentamethyltricyclodecenones, we sought to synthesize unknown *tetramethyl-norbornadiene*¹⁰ **1** (TMNBD) and to study the effect of introducing four methyl groups in the norbornadiene ring instead. We developed a scalable synthesis of TMNBD, studied its behavior toward catalytic PKr's, and assessed the reactivity of the corresponding PK adducts toward conjugate addition and rDA reactions.

Scheme 3. Preparation of TMNBD



We envisaged a Diels–Alder reaction between 1,2,3,4-tetramethylcyclopentadiene and a synthetic acetylene equivalent for the preparation of TMNBD. After much experimentation with a variety of standard dienophiles we were able to isolate the desired diene by reductive desulfonylation from adduct **3**, albeit in a disappointingly low yield (Scheme 3). We then turned our attention to 1,2-dichloroalkane precursors which are reported to undergo reductive elimination in the presence of alkaline metals.¹¹ Thus, **4** was accessed in good yield by a Diels–Alder reaction between *trans*-dichloroethylene and 1,2,3,4-tetramethylcyclopentadiene in a pressure vessel. We were unable to obtain any diene when **4** was exposed to magnesium. In contrast, reaction with lithium provided TMNBD in good yields on a multigram scale after purification by distillation. It is worth noting the importance of the lithium source on the reaction outcome. When lithium with a high sodium content was used (0.5%), an important increase in reactivity was observed, reaching total conversion after 24 h. The use of the same source of lithium for extended reaction times led only to decomposition of the desired olefin. The stereospecific nature of such eliminations also deserves a comment; early attempts to prepare **1** from *cis*-dichloro

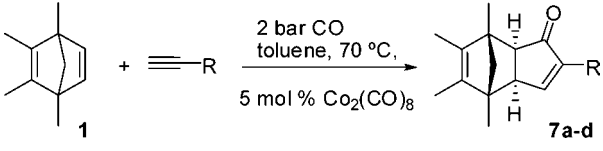
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derivative **6** (derived from the Diels–Alder adduct of vinyl carbonate) only met with failure.

Once we secured a reliable preparative synthesis of TMNBD, we started studying the behavior of this strained olefin toward catalytic PKr's with different acetylenes, using $\text{Co}_2(\text{CO})_8$ as a catalyst (Table 1). Reaction occurs exclusively at the less substituted and therefore less hindered double bond. The corresponding *exo* fused adducts were obtained in good yields. The reaction proceeds with remarkable diastereoselectivity since we were unable to isolate any of the *endo* isomers. The reaction conditions employed here would typically deliver an 85:15 diastereomeric ratio using norbornadiene instead.¹²

Table 1. Catalytic PKr's with TMNBD



	R	yield	product
1	TMS	89%	7a
2	Ph	85%	7b
3	<i>n</i> -Bu	85%	7c
4	CH_2OTBDPS	79%	7d

We then subjected trimethylsilylacetylene and *n*-butyl adducts (**7a** and **7c**) to conjugate addition with a set of different organolithium and Grignard reagents in combination with copper(I) salts, in either catalytic or stoichiometric amounts. Under these conditions the reaction yielded compounds **8a–8f** with complete diastereoselectivity. A 2D-NOESY experiment of derivative **8a** confirmed that the nucleophile attacked from the less hindered *exo* face of the cyclopentenone ring, with the TMS group adopting a *trans* arrangement with respect to the R_2 group. The α -silyl enone **7a** proved to be an excellent Michael acceptor in accordance with previous findings,¹³ and the corresponding α -silylketones were obtained in moderate to good yields (Table 2, entries 1–4). In contrast, the *n*-butyl derivative **7c** displayed more sluggish reactivity and lower yields were obtained due to the fact that total conversion was not reached (table 2, entry 5). Adduct **7e** resulting from protodesilylation of **7a** also proved to be a good substrate. Additionally, we prepared the nitro derivative **8g** by fluoride catalyzed conjugate addition of nitromethane, which occurs with simultaneous α -silyl cleavage (Table 2, entry 7).

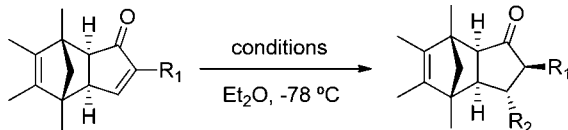
For compounds **8a–c** removal of the rather labile TMS group was carried out prior to any attempt to perform rDA

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reactions. Upon treatment with catalytic amounts of tetra(*n*-butyl)ammonium trihydrate, the α -silylketones smoothly reacted to provide substrates **9a–c** in excellent yields (Scheme 4).

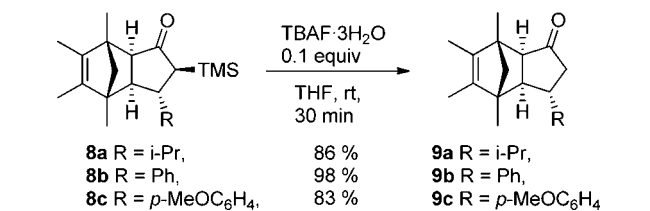
Table 2. Conjugate Additions



	conditions	yield	prod.	R_1	R_2
1	<i>i</i> -PrMgCl (1.2 equiv), CuI (0.1 equiv), Et_2O	86%	8a	TMS	<i>i</i> -Pr
2	PhMgCl (2 equiv), CuI (0.1 equiv), Et_2O	50%	8b	TMS	Ph
3	PMPMgCl (2 equiv), CuI (0.1 equiv), Et_2O	50%	8c	TMS	PMP
4	BuLi (2 equiv), CuCN (1equiv), Et_2O	60%	8d	TMS	<i>n</i> -Bu
5	MeLi (2 equiv), CuI (1 equiv), Et_2O	32%	8e	<i>n</i> -Bu	Me
6	CH_2CHMgBr (1.5 equiv), CuI (0.1 equiv), THF	78%	8f	H	vinyl
7	TBAF·3H ₂ O (0.1 equiv), CH_3NO_2	99%	8g^a	H	CH_2NO_2

^aProduct from conjugate addition and concomitant silyl cleavage.

Scheme 4. Fluoride Catalyzed Removal of the TMS Group

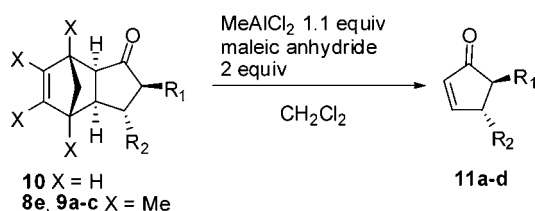


With a variety of tricyclodecenones in hand, the stage was set for the key retro-cycloaddition reaction. We initially compared the relative reactivity of adduct **9b**, containing the tetramethylnorbornene manifold, with that of the corresponding norbornene analog when subjected to rDA reaction (Table 3, entries 1 and 2). The adduct derived from norbornadiene (**10**), in the presence of methyl aluminum dichloride and maleic anhydride, required a temperature of 50 °C for the reaction to take place. In contrast, substrate **9b** reacted smoothly at only 0 °C when subjected to the same reagent combination and reaction was complete within a much shorter time. Thus, we managed to lower by some 50 °C the reaction temperature by the addition of

four methyl groups to the extruding cyclopentadiene fragment. These results are in good agreement with the ones obtained by Grieco using pentamethyl *endo*-fused cyclodecenones.⁸ This chemistry was extended to the different conjugate addition products synthesized, and we obtained good yields of the desired cyclopentenones for most substrates. Only compound **8e** with a higher substitution pattern gave a less satisfactory result (Table 3).

Thermogravimetric analysis of compounds **9a** and **10** gives us qualitative insight into the activation temperatures for the purely thermal process. Compound **10** (a liquid at rt) displays an endothermic process with an onset at 245 °C accompanied by a reduction in mass. This is ascribed to the retro-Diels–Alder decomposition into volatile fragments (cyclopentadiene, **11a**). For solid compound **9a** a first endotherm without reduction is observed at 77 °C which corresponds to the compound's melting point, and a second heat absorption with concomitant mass reduction indicating the rDA process is observed at 199 °C. The roughly 50 °C difference observed between the two reaction endotherms nicely matches the trend observed for the Lewis acid mediated reaction.

Table 3. Retro-Diels–Alder Reactions of Tricyclic Decenones

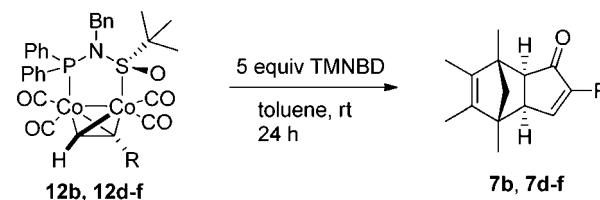


s. m.	R ₁	R ₂	X	temp, time	yield	prod.
1	10	H	Ph	H	50 °C, 1.5 h	73% 11a
2	9a	H	Ph	Me	0 °C, 0.5 h	76% 11a
3	9b	H	PMP	Me	0 °C, 0.5 h	71% 11b
4	9c	H	<i>i</i> -Pr	Me	0 °C, 0.5 h	70% 11c
5	8e	<i>n</i> -Bu	Me	Me	0 °C, 0.5 h	47% 11d

Finally, we addressed the preparation of TMNBD Pauson–Khand adducts in enantiopure form to further enhance the synthetic potential of this technology. Our research group has a long-standing experience in

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Table 4. Enantioselective Pauson–Khand Reactions



complex	R	yield	ee	prod.	
1	12b	Ph	94%	99%	(–)- 7b
2	12d	CH ₂ OTBDPS	80%	94%	(–)- 7d
3	12e	CH ₂ NHBoc	95%	94%	(–)- 7e
4	12f	4-F-Ph	77%	98%	(–)- 7f

asymmetric PKr's, for which we rely on an extended inventory of purpose-designed chiral ligands.¹⁴ Cobalt complexes **12b** and **12d–f** featuring our *N*-phosphino-*tert*-butylsulfonamide chiral ligand^{14d} were subjected to reaction with excess TMNBD to provide the corresponding Pauson–Khand adducts in excellent yields and enantioselectivities (Table 4).

In conclusion, we have developed a reliable and versatile sequence toward substituted cyclopentenones using an optimized retro-Diels–Alder reaction as the key step. With easy access to multigram quantities of diene **1**, a myriad of PKr-conjugate addition combinations can be envisaged providing an equally vast number of cyclopentenone precursors. TMNBD derivatives display exquisite reactivity in the rDA reactions which anticipate the success of this strategy with more functionalized substrates. With homochiral Pauson–Khand precursors at hand, this technology can eventually be applied to efficient and modular syntheses of biologically relevant products, such as prostaglandins and analogues.

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Supporting Information Available. Experimental procedures, spectral and analytical data for all new compounds. Thermogravimetric analysis of **9a** and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.