Design and synthesis of (*E*)-1-((3-ethyl-2,4,4-trimethylcyclohex-2-enylidene)methyl-4-substituted benzenes from 1-(2,6,6-trimethylcyclohex-1-enyl)ethanol†

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A novel strategy for synthesizing (*E*)-1-((3-ethyl-2,4,4-trimethylcyclohex-2-enylidene)methyl-4-substituted benzenes from 1-(2,6,6-trimethylcyclohex-1-enyl)ethanol 3 has been developed; the allylic alcohol 3 was treated with PPh_3·HBr in methanol followed by aldehydes in the presence of a base and furnished the 1,3-dienes in moderate to good yields (79–86%).

In the context of an ongoing chemical biology project, studying the role of retinoic acid signaling pathways during zebrafish embryogenesis, we synthesized novel retinoid libraries. Retinoids (retinoic acid analogues) play key roles in embryogenesis and for maintenance of various cellular processes such as cell growth and differentiation.[1] Retinoids also have clinical value for cancer chemoprevention and therapy, although their use is limited by toxicity and teratogenecity at pharmacological doses.[2] Retinoids exert their biological effects by activating nuclear receptors and modulating gene transcription.[3] A clear understanding of the biological roles of the retinoid receptor families would greatly facilitate the design of retinoid analogues that could be targeted for specific diseases to improve the therapeutic index.[4] A number of synthetic retinoids have been synthesized that interact selectively with its receptors.[5] Understanding the importance of the retinoids we were keen to synthesize compounds **1a–c** as new retinoic acid analogs by introducing a constrained phenyl ring system in the place of conjugated alkene backbone (spacers). In the process of synthesizing compound **1a**, we encountered an unusual Wittig salt formation from the allylic alcohol **3** which involved the formation of the unusual 1,3-diene **2** when the Wittig ylide **4** was treated with aldehyde **5**.[6]

The regio- and stereospecific synthesis of 1,3-dienes is of great importance in synthetic organic chemistry due to the frequent occurrence of these fragments in biologically active natural products, as well as to their utilization in numerous transformations such as the Diels–Alder reaction.[7,8] Electrocyclizations of conjugated trienes offer a powerful ring-forming strategy, with the creation of one or two new stereocenters.[9–12] Realizing the importance of 1,3-dienes and our novel finding to synthesize 1,3-dienes from allylic alcohol **3**, prompted us to explore this result to synthesize 1,3-dienes and trienes. We wish to report the reaction of unusual phosphonium ylide **4** with aldehydes in presence of base offers an efficient, direct route to a number of highly substituted 1,3-dienes. Our original goal was to synthesize compounds **1a–c** (Fig. 1) as new retinoic acid analogs by introducing constraints *via* a phenyl ring.

In the process of synthesizing **1a**, from **3**, we encountered the unusual Wittig salt **4** (Scheme 1), which led to the formation of the unusual 1,3-diene **2** when the ylide **4** was treated with aldehyde **5**.[6]

The unusual formation of **2** prompted us to explore the reaction in further detail in an effort to develop a novel strategy for synthesizing substituted 1,3-dienes and 1,3,5-trienes. We quickly discovered that the initial reaction conditions were not optimal for synthesizing 1,3-dienes (Table 1, entry 1). Using 4-formylbenzoic acid methyl ester **5** as a model aldehyde, all reaction parameters were reinvestigated. Representative examples of solvent, base, reaction time and temperature studies are listed in Table 1. The solvent and the base are crucial in achieving high yields. DMF and sodium

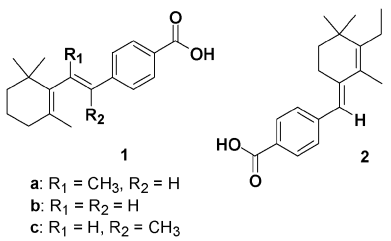
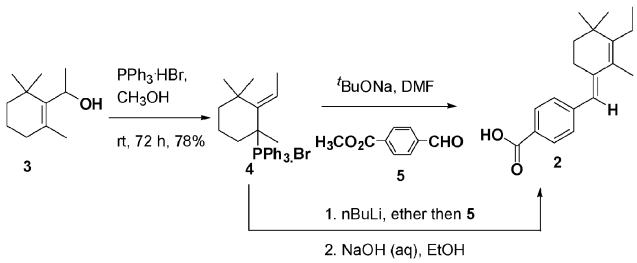


Fig. 1



Scheme 1

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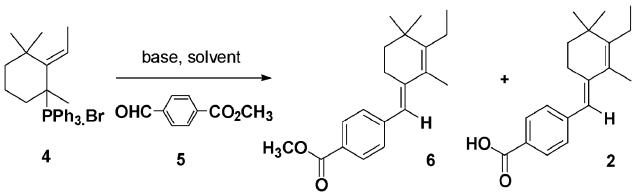
† Electronic supplementary information (ESI) available: Complete experimental procedures and characterization data for all new compounds. See DOI: 10.1039/b823063c

Table 1 Optimization of 1,3-diene reaction parameters



Entry	Solvent	Base	T/°C	t/h	Yield (%) 6	2
1	Et_2O	^{n}BuLi	−78 to RT	30	85	0
2	DMF	^{t}BuONa (1.1 equiv.)	RT	24	50	25
3	DMF	^{t}BuONa (2 equiv.)	RT	20	50	25
4	DMF	^{t}BuONa (2.5 equiv.)	RT	12	20	65
5	DMF	^{t}BuONa (3 equiv.)	RT	12	0	85

tert-butoxide at room temperature provided the optimal conditions for generating **2** in high yield. It is noteworthy that three equivalents of sodium *tert*-butoxide leads to the highest yield of **2** (entry 5) in a one-pot Wittig reaction, followed by ester hydrolysis.

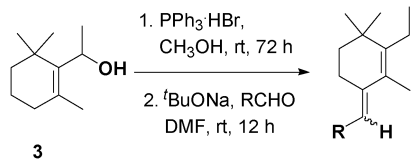
The structure of **2** was confirmed by NMR (^{1}H, ^{13}C, NOE) experiments and HRMS. The resonance at δ 2.19 (q, 2H) in the ^{1}H NMR and at δ 22.3 in the ^{13}C NMR are characteristic for the methylene in an ethyl sidechain attached to the cyclohexene ring. NOE experiments clearly indicate that the phenyl ring is *trans* in **2** (^{1}H–^{1}H NOEs, δ/ppm: 6.46 → 7.38 (4%), 6.46 → 1.85 (18%), 7.39 → 7.90 (7%), 7.39 → 6.46 (4%), 7.39 → 2.55 (1%), see ESI†).

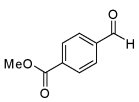
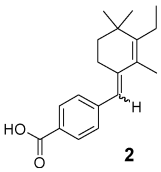
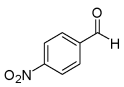
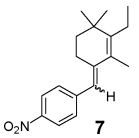
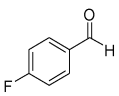
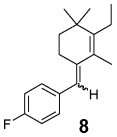
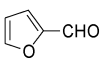
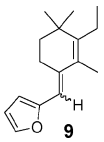
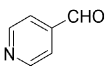
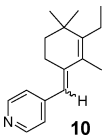
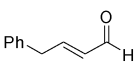
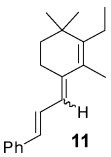
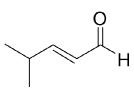
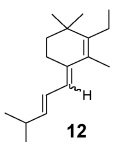
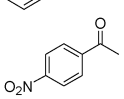
We next examined the scope of the reaction with a variety of different aldehydes (Table 2). The reaction proved tolerant of an electron-withdrawing (*p*-NO_2, entry 2; Table 2) and -donating (*p*-F, entry 3; Table 2) on the phenyl ring of the aldehyde. To prove that our new method can be successfully applied to the five-membered ring conjugate, we chose a furfural as one of the substrates (entry 4; table 2). This gave the corresponding product with 79% yield. The same trend was observed with 4-pyridinecarbaldehyde (entry 5; Table 2), and the reaction gave the corresponding 1,3-diene conjugate with pyridine moiety in good yield (83%). Besides the aromatic aldehydes, the α,β-unsaturated aldehydes (entries 6 and 7; Table 2) proved more interesting, and we isolated the corresponding 1,3,5-trienes in good yields. When ketones were used as carbonyl compounds (entries 8 and 9, Table 2), no desired compounds were isolated even at reflux condition for 2 days.

In an attempt to reduce the number of synthetic steps, we evaluated the feasibility of a one-pot reaction (Scheme 2). Gratifyingly, the one-pot conversion of allylic alcohol **3** to the 1,3-diene acid **2** was successful, affording the desired product in 13 and 52% yields in CH_3OH and DMF, respectively. Most importantly, the direct Wittig reaction of the unusual Wittig salt with 4-formylbenzoic acid affords **2** in 78% yield (Scheme 3). This process has potential application in industry to synthesize products on a gram scale.

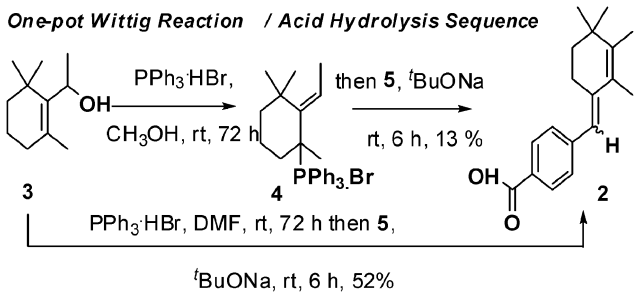
A reasonable mechanism for the syntheses of 1,3-dienes and 1,3,5-trienes is presented in Scheme 4. The bromination of allylic alcohol **3** and addition of PPh_3 is envisioned to give the unusual quaternary Wittig ylide **4**, which then converts to a secondary phosphonium ylide **C** by treatment with base (^{n}BuLi or ^{t}BuONa). **C** then undergoes an intramolecular H^+

Table 2 Synthesis of substituted 1,3-dienes; unusual Wittig reaction of allylic alcohol **3**[a]

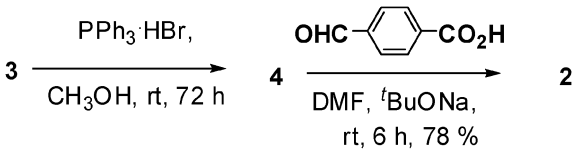


Entry	RCHO	Product	E : Z[b]	Yield[c] (%)
1		 **2**	1 : 0	85
2		 **7**	1 : 0.46	80
3		 **8**	1 : 0.05	78
4		 **9**	1 : 0[d]	79
5		 **10**	1 : 0[d]	83
6		 **11**	1 : 0[d]	86
7		 **12**	1 : 0[d]	81
8		—	—	0
9		—	—	0

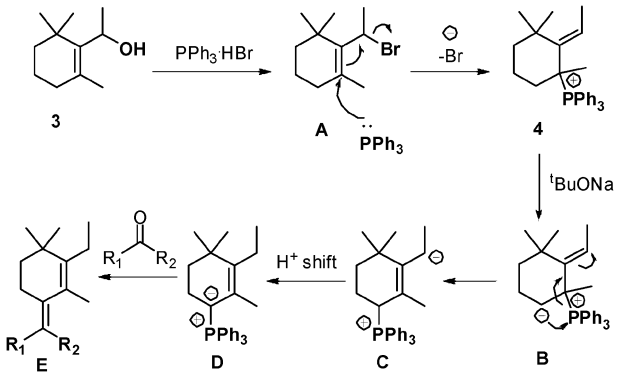
[a] All reactions were performed on 1 mmol of aldehyde with 3 equiv. of ^{t}BuONa in DMF for 12 h. [b] The E : Z ratio was determined by ^{1}H NMR. [c] Isolated yield refers to aldehyde. [d] Trace amount of Z isomer was observed in ^{1}H NMR.



Scheme 2 One-pot Wittig reaction and acid hydrolyis.



Scheme 3 One-pot Wittig reaction with 4-formylbenzoic acid.



Scheme 4 Proposed reaction mechanism.

shift to provide **D**, which subsequently reacts with aldehydes to furnish dienes **E**. (see ESI† for other mechanisms).

In support of the postulated mechanism, we isolated one of the intermediates **4**. It is interesting to point out that the olefinic peaks (δ 5.50–5.70) in ^{1}H NMR spectrum of intermediate **4** (Fig. 3, ESI†) provides evidence that the triphenylphosphine added to the olefinic double bond of **A** *via* a simple allylic type displacement of bromine. To the best of our knowledge, this is the first Wittig reaction of this type to be reported in an allylic alcohol system.

In conclusion, we have developed a general and flexible approach to highly substituted 1,3-dienes and 1,3,5-trienes. The ready availability of the starting materials and the simplicity of the reaction conditions make this a very attractive protocol for generating valuable building blocks in polyene syntheses. The variety of substituents in the phenyl ring, the possible application to five-membered heteroaromatics, and the extension to conjugated dienes make this method valuable in the synthesis of small molecules and natural products. Preliminary attempts to carry out Diels–Alder chemistry using the 1,3-dienes as well as 6π electrocyclization of the 1,3,5-trienes and their biological study in zebrafish embryogenesis are under way.

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