

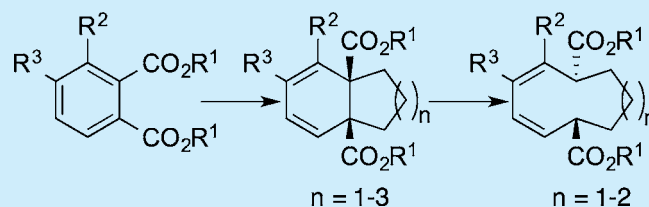
A Two-Step, Stereoselective Synthesis of Nine- and Ten-Membered Carbocycles from Phthalates

Gustavo Prado, Alberte X. Veiga, Fernando Fernández-Nieto, M. Rita Paleo,* and F. Javier Sardina*

Departamento de Química Orgánica and Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Supporting Information

ABSTRACT: A two-step, stereoselective procedure for the synthesis of nine- and ten-membered carbocycles from readily available phthalates is described. A variety of dialkyl phthalates have been transformed into $[6,n]$ -fused bicyclo systems ($n = 5, 6, 7$) by a dearomatization/cyclization process and then converted into cyclonona- and cyclodecadienes through a bond cleavage reaction, whereby both processes are promoted by alkaline metals in THF.



The development of practical methods for the synthesis of nine- and ten-membered carbocycles is still challenging.¹ Despite the different strategies that have been explored for this purpose, such as transition-metal-catalyzed cycloaddition reactions,² fragmentations³ and ring expansions,⁴ cyclizations,⁵ ring-closing metathesis,⁶ and oxygen-bridge templating approaches,⁷ among others,⁸ there is still a need for developing synthetic methods that provide these molecules in a few steps from readily available starting materials. We report herein our serendipitous discovery of a two-step preparation of nine- and ten-membered carbocycles from inexpensive phthalates, which involves the use of alkali metals in both steps.

We are interested in exploiting dearomatization reactions to build complex structures from inexpensive and readily available aromatic compounds. In this context, we have already reported on a one-step dearomatization–annulation protocol that affords fused bicyclic compounds from the reaction of aromatic diesters with tin nucleophiles, followed by trapping of a *bis*-enolate intermediate species with primary *bis*-electrophiles.^{9,10} Unfortunately, the synthetic potential of this transformation is diminished by the toxicity and high cost of the required organotin compounds, even though we found conditions to perform the reaction using substoichiometric amounts of tin reagents.^{9a} For an unrelated project, we developed the reduction of dimethyl anthracene-9,10-dicarboxylate with lithium/naphthalene under ammonia-free Birch conditions,¹¹ which generated a stable *bis*-enolate. Dialkylation of this intermediate gave medium- and large-ring dibenzo[*n*.2.2]-carbocycles.¹² By combining the rationale from these two projects, we decided to investigate the possibility of generating *bis*-enolates from phthalates under reductive conditions, thus avoiding the use of hazardous tin reagents, and to further explore the chemistry of these species, pursuing access to fused bicyclic compounds. We were pleasantly surprised when our studies in this area uncovered, additionally, that these latter compounds underwent a facile bond-cleavage reaction under reductive conditions, to give medium-sized carbocycles.¹³

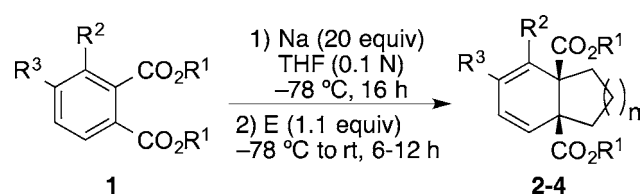
For the initial investigation on the reductive alkylation, we chose diisopropyl phthalate as the starting aromatic diester, lithium metal as the reductant, and 1,3-dibromopropane as the electrophile. When an excess of lithium metal in THF was used as the reducing agent, the ensuing reaction was very slow and only low conversions (15–20%) to the desired product **2a** were achieved. Sodium proved to be a more efficient reductant than lithium. Thus, when **1a** was treated with sodium metal in THF for 16 h at $-78\text{ }^{\circ}\text{C}$, and the intermediate *bis*-enolate was quenched with 1,3-dibromopropane, the desired bicycle **2a** was isolated in 92% yield. The *cis*-stereochemistry of the product was assigned by comparison with the product obtained via stanna-Brook rearrangement.^{9b} Isopropyl esters were the best substrates for this reaction, although methyl (70% yield) and *tert*-butyl (85% yield) esters worked well too (entries 1–3, Table 1).

This reaction tolerates the presence of substituents on the aromatic ring, although at the cost of a considerable rate reduction, making it necessary to add naphthalene as an electron carrier to obtain complete conversions.¹⁴ The corresponding products **2d–h** were isolated in moderate to good yields (see entries 4 to 8, Table 1). The presence of a methyl group at C-3 causes a significant drop in the yield (**2d**, 56%) when compared to its C-4 isomer (**2e**, 75%), probably due to destabilization of the intermediate *bis*-enolate by steric compression. Halogen-substituted phthalates afforded only decomposition products.

Variations in the nature and the length of the chain of the *bis*-electrophile were also well tolerated. Thus, the *exo*-methylene bicyclo[4.3.0]nonane **2i** was easily prepared in 60% yield when 3-chloro-2-chloromethyl-1-propene was used as the electrophile. Functionalized and unfunctionalized bicyclo[4.4.0]decadienes **3** and bicyclo[5.4.0]undecadienes **4**

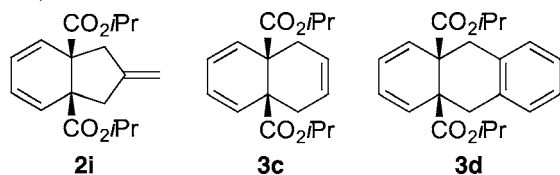
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Table 1. Synthesis of Fused Bicyclic Systems by Reductive Alkylation¹⁵


entry	R ¹	R ²	R ³	E	n	product	yield
1	<i>i</i> Pr	H	H	Br(CH ₂) ₃ Br	1	2a	92%
2	Me	H	H	Br(CH ₂) ₃ Br	1	2b	70%
3	<i>t</i> Bu	H	H	Br(CH ₂) ₃ Br	1	2c	85%
4	<i>i</i> Pr	Me	H	Br(CH ₂) ₃ Br	1	2d	56% ^a
5	<i>i</i> Pr	H	Me	Br(CH ₂) ₃ Br	1	2e	75% ^a
6	Me	H	OMe	Br(CH ₂) ₃ Br	1	2f	55% ^a
7	Me	H	CO ₂ Me	Br(CH ₂) ₃ Br	1	2g	30% ^a
8	<i>i</i> Pr	H	CO ₂ <i>i</i> Pr	Br(CH ₂) ₃ Br	1	2h	48% ^a
9	<i>i</i> Pr	H	H	H ₂ C=C(CH ₂ Cl) ₂		2i	60% ^b
10	<i>i</i> Pr	H	H	Br(CH ₂) ₄ Br	2	3a	88%
11	<i>t</i> Bu	H	H	Br(CH ₂) ₄ Br	2	3b	87%
12	<i>i</i> Pr	H	H	MsO-CH=CH-OMs		3c	55%
13	<i>i</i> Pr	H	H	<i>o</i> -xylene- α,α' -diOMs		3d	48%
14	<i>i</i> Pr	H	H	I(CH ₂) ₅ I	3	4a	76%

^a(1) Na (10 equiv), naphthalene (0.6 equiv), $-50\text{ }^{\circ}\text{C}$, 6 h; (2) E (1.1 equiv), $-50\text{ }^{\circ}\text{C}$ to rt, 12–16 h. ^bE dissolved in DMF (0.55 M), $-78\text{ }^{\circ}\text{C}$ to rt, 24 h.

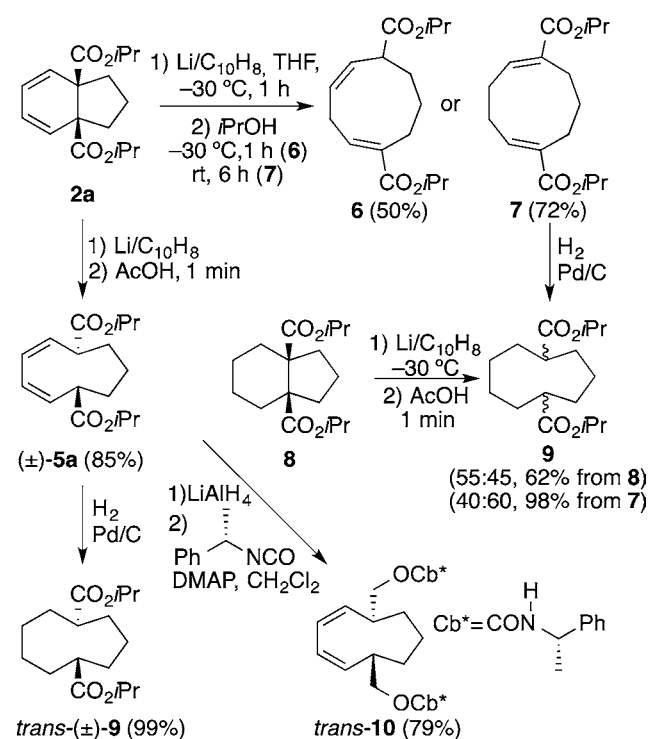


were also prepared in good yields (entries 10–14, Table 1). Remarkably, the cyclization to a seven-membered ring occurred uneventfully, provided that the temperature of the reaction mixture was allowed to reach $35\text{ }^{\circ}\text{C}$. Thus, bicyclo[5.4.0]undecadiene **4a** was isolated in 76% yield when using 1,5-diiodopentane as the electrophile. These results confirm that the reductive alkylation of phthalates is a general process that allows for the preparation of a variety of [6,5]-, [6,6]-, and [7,6]-fused bicycles using a reducing agent, sodium or sodium/naphthalene, and a suitable *bis*-electrophile.

With an ample supply of fused bicycles **2–4**, we decided to explore their use in the preparation of propellane structures. For our first foray into these types of transformations we explored the acyloin condensation of the ester groups of bicyclo[4.3.0]nonane **2a**. But to our surprise and delight, when **2a** was treated with Li/naphthalene in THF at $-30\text{ }^{\circ}\text{C}$, we isolated a mixture of cyclononadienes **5a** and **6** and none of the expected acyloin products, after quenching with *i*PrOH. We surmised that the C–C bond of the vicinal diesters of bicyclo[4.3.0]nonane **2a** had been reductively cleaved to give a nine-membered *bis*-enolate, which then had been doubly protonated upon quenching of the reaction, affording a mixture of kinetic and thermodynamic protonation products. There are precedents for this kind of reductive cleavage of 1,2-diester,¹³

but the mechanistic picture of this reaction and, especially, the involvement of enolate intermediates has not been studied.

If a *bis*-enolate, most probably formed by bond cleavage of a dianion diradical (a diketyl) species,^{13a} is an intermediate in this transformation, then choosing the right protonation conditions should allow us to selectively obtain products of protonation under kinetic or thermodynamic conditions. In fact, after some experimentation, we found optimized conditions for the selective preparation of cyclononadienes **5a**, **6**, and **7** (Scheme 1). Unconjugated cyclononadiene **5a** was obtained in excellent

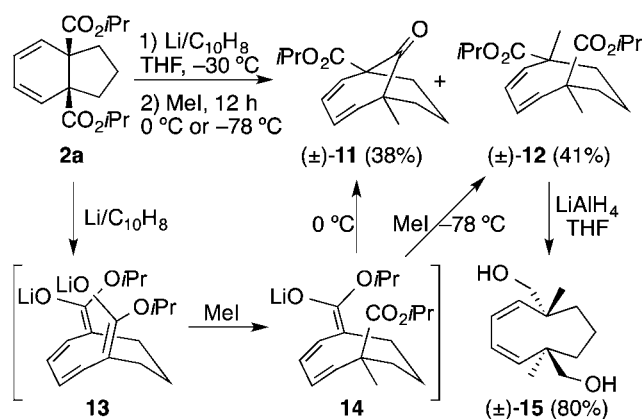
Scheme 1. Regioselective Ring-Opening Reaction


yield (85%) when the reaction was quenched with AcOH at $-30\text{ }^{\circ}\text{C}$ for just 1 min. In contrast, quenching the reaction with *i*PrOH (1 h at $-30\text{ }^{\circ}\text{C}$) gave solely monoconjugated cyclononadiene **6** (50% yield). Moreover, when the reaction was quenched with *i*PrOH at $-30\text{ }^{\circ}\text{C}$ and then stirred for 6 h at rt, the doubly conjugated cyclononadiene **7** was isolated as the single reaction product (72% yield).

Remarkably, this cleavage–protonation reaction of bicyclic dienes **2** proceeds with complete stereoselection, as established by the comparison of the ¹³C NMR spectrum of the hydrogenation product of **5a** (which showed signals for only one stereoisomer), with that of the ring-opening product of the saturated hydrindane **8** (which gave a 55:45 mixture of diastereomers of **9**, readily distinguishable by ¹³C NMR), and that of the hydrogenation product of *bis*-unsaturated diester **7**, which also afforded a mixture of diastereoisomers of **9** (Scheme 1). To figure out the relative stereochemistry of the stereogenic centers of diene **5a**, we transformed it into a crystalline derivative by a two-step procedure: LiAlH₄ reduction of **5a** to the corresponding diol and its subsequent derivatization with (*S*)-(–)- α -methylbenzyl isocyanate and DMAP in CH₂Cl₂ (79% yield, 2 steps). X-ray crystallographic analysis of carbamate **10** showed a *trans* disposition of the side chains.¹⁶

If the ring-opening reaction indeed takes place to give a *bis*-enolate intermediate that then undergoes stereoselectively protonation, then chances are that it could also be stereoselectively alkylated with an appropriate electrophile. In fact, when we treated bicycle **2a** with Li/naphthalene in THF at $-30\text{ }^{\circ}\text{C}$ and then trapped the intermediate with methyl iodide, a 1:1 mixture of compounds **11** and **12** (Scheme 2) was formed.

Scheme 2. Stereoselective Ring Opening/Alkylation

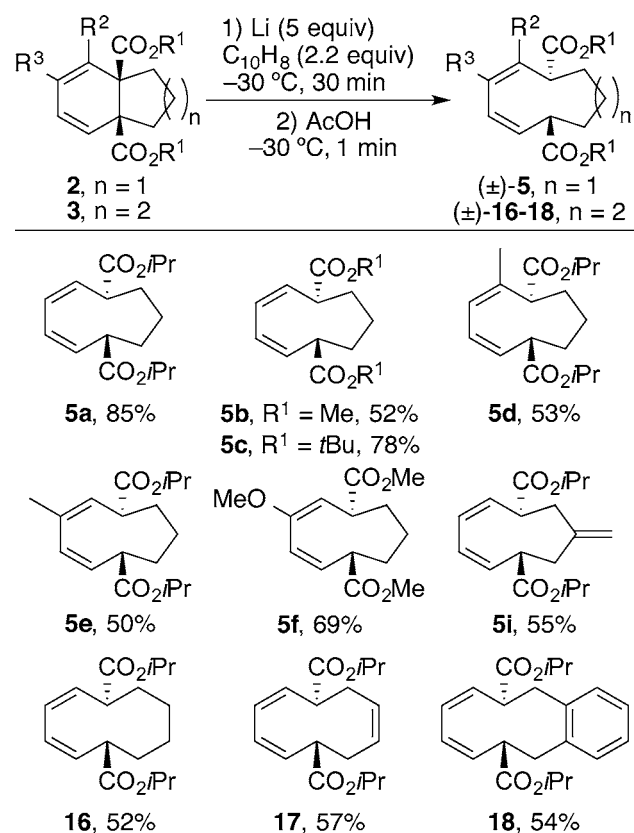


Both products are derived from the monoalkylation of the intermediate *bis*-enolate **13**, to give mono-enolate **14**, which can then evolve through a Dieckmann condensation to give bicyclo **11**, or through a further methylation to yield nonadiene **12**. The selectivity of the reaction could be somewhat steered by changing the reaction temperature: when the reaction was run at $-78\text{ }^{\circ}\text{C}$ dimethylcyclohexadiene **12** was the major product (6:1 ratio of **12** and **11**), while at $0\text{ }^{\circ}\text{C}$ bicyclic **11** was the preferred product (4:1 ratio of **11** and **12**). The relative configuration of the stereogenic centers of **12** was determined to be *trans* by X-ray diffraction analysis of diol **15**, obtained by LiAlH₄ reduction of **12** (80%).

To delineate the scope of the stereoselective ring-cleavage–protonation sequence, the optimized reaction conditions for the synthesis of kinetic cyclohexadiene **5a** were applied to several bicyclic dienes (**2–3**) (Scheme 3). The main conclusions of this study are (i) the reaction tolerates different esters, but the isopropyl (85% yield) is more convenient than the methyl (52%) or *tert*-butyl (78%) groups; (ii) the presence of a methyl substituent in the cyclohexadiene ring causes a drop in yield (**5d** and **5e** were isolated in 53% and 50% yields, respectively); and (iii) the presence of an exo methylene in the 5-membered ring does not interfere with the bond cleavage (**5i** was obtained in 55% yield, similarly to other unsaturated substrates, such as **17** and **18**).

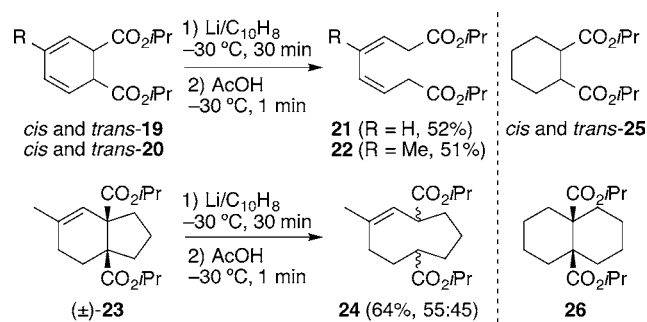
The bond cleavage reaction is not limited to the bicyclo[4.3.0]nonanes, as 10-membered carbocyclic dienes could also be prepared from 6,6-fused bicycles (Scheme 3). Thus, when bicycle **3a** was treated with lithium/naphthalene at $0\text{ }^{\circ}\text{C}$ for 1 h, and then quenched with AcOH for 1 min at the same temperature, cyclodecadiene **16** was isolated in 52% yield as the sole reaction product. A similar result was obtained from bicyclic compound possessing further unsaturation (**3c** led to cyclodecatriene **17** in 57% yield) or substitution (which allowed the preparation of **18** from **3d** in 54% yield). Unfortunately all attempts to prepare 11-membered ring dienes starting from the corresponding bicyclo[5.4.0]undecadiene **4a** have been unsuccessful to date.

Scheme 3. Stereoselective Reductive Ring Opening to 9- and 10-Membered Carbocycles



In an attempt to gain mechanistic insights into this transformation and to pinpoint which are the precise structural requirements for the ring-opening reaction to be successful, a series of diesters (see Scheme 4) were treated with Li/

Scheme 4. Scope of Substrates for Ring-Opening Reactions



naphthalene, followed by protonation with acetic acid. Cyclohexadiene diesters (*cis*-**19**, *trans*-**19**, *cis*-**20**, and *trans*-**20**), all reacted separately were successfully opened (to give **21** or **22**) in similar yields, showing that the cleavage is not sensitive to stereoelectronic effects. In stark contrast, no ring-opened product was observed from saturated diisopropyl cyclohexane-1,2-dicarboxylates **25**. Thus, the stability of the intermediate *bis*-enolate seems to be the determining factor in the success of the reaction. The unconjugated, less stable *bis*-enolate which should be formed from the saturated esters **25** appears to be inaccessible under our reaction conditions.

Strain release also appears to play a role in facilitating the bond cleavage, as monounsaturated and saturated bicyclic 6,5-

fused systems **23** and **8** also underwent cleavage (to **24** and **9**, respectively, isolated as 55:45 stereoisomeric mixtures), but the less strained saturated 6,6-bicyclic compound **26** did not.

In summary, we have developed a straightforward, two-step, stereoselective synthesis of functionalized nine- and ten-membered carbocycles from phthalates, mediated by alkali metals. Further studies to understand and exploit the stereoselectivity of the ring-opening process are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, and X-ray crystallographic data of compounds **10** and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: rita.paleo@usc.es.

*E-mail: javier.sardina@usc.es.

Notes

The authors declare no competing financial interest.

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(15) The use of mesylates affords similar yields to bromides.

(16) The two *trans* diastereomers displayed only one set of signals in the ¹H and ¹³C NMR spectra.