

A highly efficient total synthesis of (*R*)-(+)-muscopyridine by intramolecular [4+2] cycloaddition of bisketene

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Received 30 November 2007; revised 17 December 2007; accepted 20 December 2007

Available online 25 December 2007

Abstract

A highly efficient total synthesis of (*R*)-(+)-muscopyridine **1** has been accomplished in 12 steps with 40% overall yield. A highlight of the synthesis is the intramolecular [4+2] cycloaddition of bisketene to afford a bridged pyrone and ring transformation of the pyrone to afford pyridine derivatives.

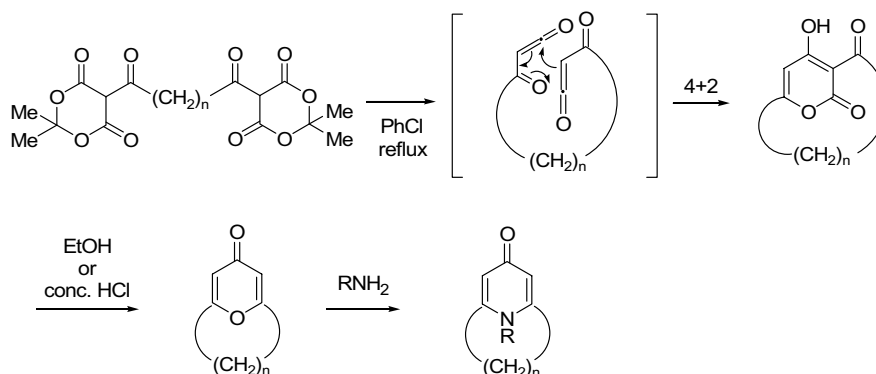
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Keywords: Intramolecular cycloaddition; Bisketene; Ring transformation; Muscopyridine

The design and synthesis of cyclophanes, macrocycles containing aromatic or heteroaromatic groups, is a fascinating branch of organic chemistry.^{1,2} Recently, we have developed a convenient method for synthesizing cyclophanes by the intramolecular [4+2] cycloaddition of bis(acylketene), which is generated from bis(4,6-dioxo-1,3-dioxane) in refluxing chlorobenzene.³ Furthermore,

we reported the efficient and unique synthetic method of *meta*-pyridinophanes using this ketene cycloaddition methodology (Scheme 1).⁴

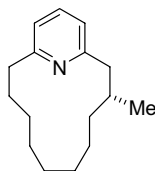
The *meta*-pyridinophane derivative (*R*)-(+)-muscopyridine **1** is one of the odoriferous constituents of natural musk obtained from the male musk deer *Moschus moschiferus* (Fig. 1). Its empirical formula was determined by



Scheme 1. Ketene cycloaddition methodology for synthesizing cyclophanes.

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Fig. 1. (R)-(+)-muscovopyridine **1**.

Ruzicka and Prelog⁵ in 1946. Despite its rather simple structure, **1** is a fascinating and repeated target for a total synthesis.^{6–8} In this study, we report an application of the ketene cycloaddition methodology to the highly efficient synthesis of compound **1**.

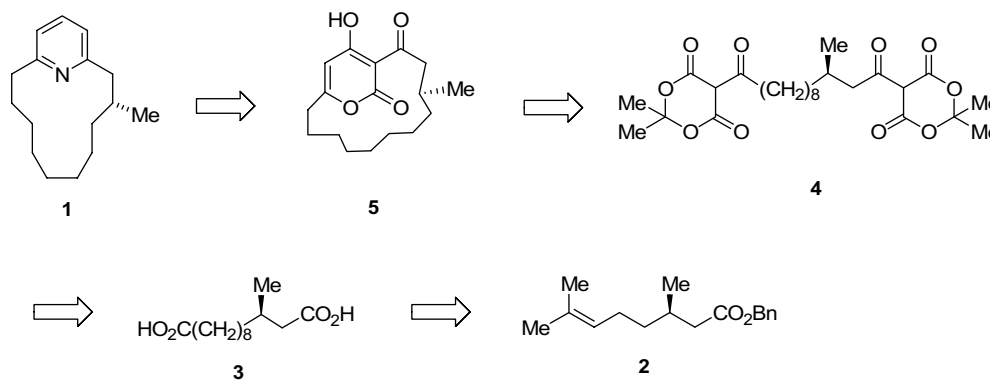
We envisaged the application of the ketene methodology to the synthesis of muscovopyridine **1**, as illustrated in Scheme 2. The pyridine ring of **1** would be accessible by the ring transformation of *para*-cyclophane **5**, which we plan to obtain from bis(4,6-dioxo-1,3-dioxane) **4** through an intramolecular cycloaddition of bis(acylketene).³ **4** can be derived from the chiral dicarboxylic acid **3**, which can be obtained from benzyl (*R*)-citronellate **2**. Compound **2** is readily synthesized from the commercially available (*R*)-(+)-citronellic acid.^{9,10}

The synthesis of **3** was commenced with the epoxidation of the olefinic benzyl ester **2** with *m*-CPBA to provide epoxide **6** in 98% yield as a mixture of diastereomers (Scheme 3). The ring opening reaction of **6** to yield diol **7**, followed by the oxidative cleavage of **7** with NaIO₄, quantitatively

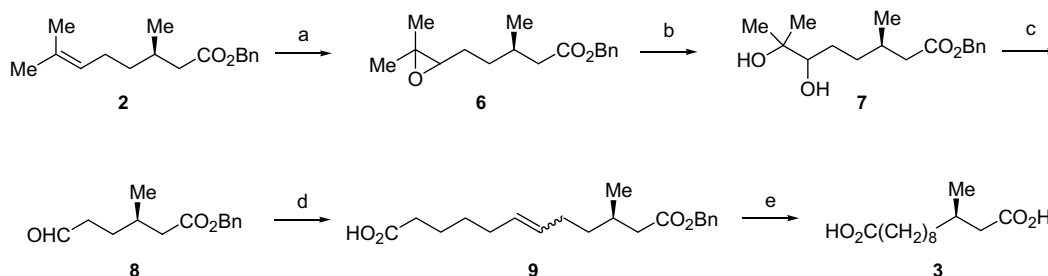
afforded aldehyde **8**. The Wittig reaction of **8** with phosphonium salt **10**¹¹ provided the olefinic acid **9** in 76% yield, which was hydrogenated to afford **3** in 99% yield.

para-Cyclophanes **5a,b** were prepared from **3** in three steps.³ Intermediate **4**, obtained by condensation of dicarboxylic acid dichloride derived from **3** with two molecules of Meldrum's acid, was heated in refluxing chlorobenzene to generate bisketene **10**, which in situ underwent intramolecular cycloaddition to afford **5a,b** in 96% yield as a 1:1 mixture of isomers (Scheme 4).

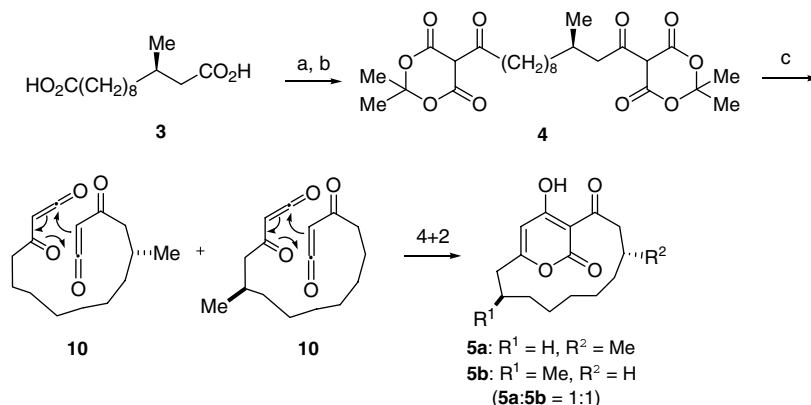
It has been reported that dehydroacetic acid is transformed into 2,6-dimethyl-4-pyrone on heating with concd HCl,^{12,13} and the pyrone ring is converted into a pyridine ring by heating with ammonia.^{12,14} We have applied this ring transformation to the synthesis of *meta*-pyridinophane from *para*-cyclophane.⁴ It was anticipated that both the isomers of *para*-cyclophanes **5a,b** would be transformed into 4-pyrone **11**. Therefore, **5a,b** were subjected to the transformation as a mixture. On heating with concd HCl, **5a,b** were transformed into **11** in 89% yield. A solution of **11** in



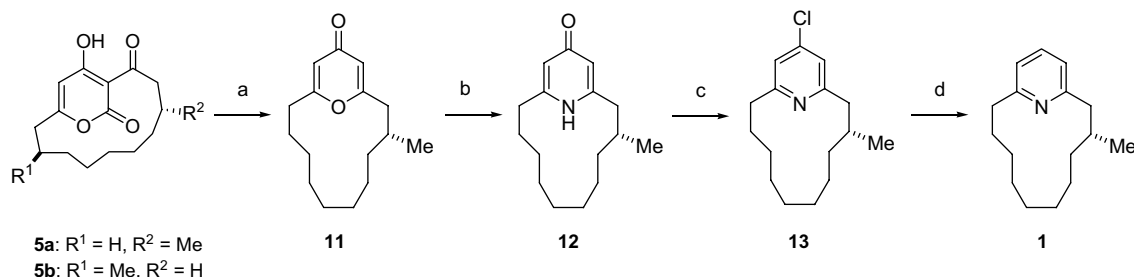
Scheme 2. Retrosynthesis of muscovopyridine.



Scheme 3. Reagents and conditions: (a) *m*-CPBA, CH₂Cl₂, 0 °C, 1 h then rt, 10 h, 98%; (b) H₂SO₄, Et₂O/H₂O, quant.; (c) NaIO₄, Et₂O/H₂O, rt, 1 h, quant.; (d) BrPPh₃(CH₂)₅CO₂H (**10**), *t*-BuOK, THF, 0 °C, 1 h then rt, 30 h, 76%; (e) H₂, Pd(OH)₂, AcOEt, rt, 12 h, 99%.



Scheme 4. Reagents and conditions: (a) SOCl_2 , reflux, 30 min; (b) Meldrum's acid, DMAP, CH_2Cl_2 , 0 °C, 2 h then rt, 1 h; (c) PhCl , reflux, 20 h (three steps, 84%).



Scheme 5. Reagents and conditions: (a) concd HCl , reflux, 12 h, 89%; (b) NH_3 , EtOH, sealed tube, 140 °C, 3 d, 87%; (c) POCl_3 , reflux, 1 h, 93%; (d) $\text{H}_2/\text{Pd-C}$, AcONa, rt, 12 h, 89%.

ethanol saturated with ammonia at 0 °C was heated in a stainless sealed tube at 140 °C for 3 days to afford pyridine **12** in 87% yield. The chlorination of **12** afforded chloropyridine **13** in 93% yield. The subsequent hydrogenation of **13** afforded the target muscopyridine **1** in 89% yield (Scheme 5). Since the starting (*R*)-citronellic acid is 98% ee and intermediate dicarboxylic acid **3** was purified by recrystallization, this compound would be >98% ee. The synthetic muscopyridine¹⁵ exhibited properties identical to those reported previously.^{5,6a,7b} The total number of steps leading to **1** was 12 with 40% overall yield, while the synthesis by Hagiwara^{7b} and Fürstner^{7c} resulted in overall yields of 7% and 19% in 12 and 11 steps, respectively.

In summary, our research involves an efficient synthetic route to (*R*)-(+)-muscopyridine from the readily available benzyl (*R*)-citronellate **2**. Our synthesis has been completed in 12 steps with 40% overall yield, which is the best yield ever reported in syntheses of (*R*)-(+)-muscopyridine. The present synthesis demonstrates that this ketene cycloaddition methodology followed by ring transformations is efficient and practical for constructing 2,6-bridged pyridines.

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- was purified by silica gel column chromatography to afford **2** (7.54 g, quant.) as a colorless oil.
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 15. Analytical data of **1**: $[\alpha]_{\text{D}}^{23} +13.1$ (c 0.50, CHCl_3), lit.,⁵ $[\alpha]_{\text{D}}^{23} +17.4$ (c 1.92, CHCl_3), lit.,^{6a} $[\alpha]_{\text{D}}^{25} +13.3$ (c 0.90, CHCl_3), lit.,^{7b} $[\alpha]_{\text{D}}^{23} +12.5$ (c 1.80, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ : 1.06 (d, 3H, $J = 6.8$ Hz), 0.86–1.34 (m, 13H), 1.79–1.83 (m, 2H), 2.02–2.07 (m, 1H), 2.54 (dd, 1H, $J = 13.0, 10.1$ Hz), 2.82–2.89 (m, 2H), 6.96 (dd, 2H, $J = 7.5, 2.0$ Hz), 7.50 (t, 1H, $J = 7.5$ Hz).