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

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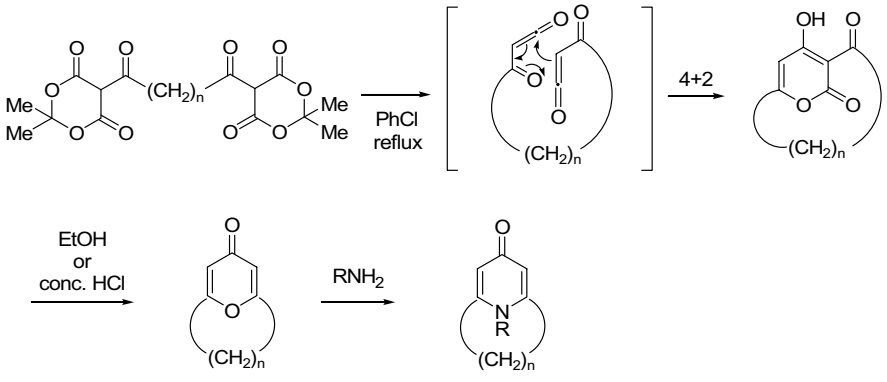
Abstract

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.

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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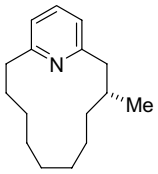


Fig. 1. (*R*)-(+)-muscopyridine **1**.

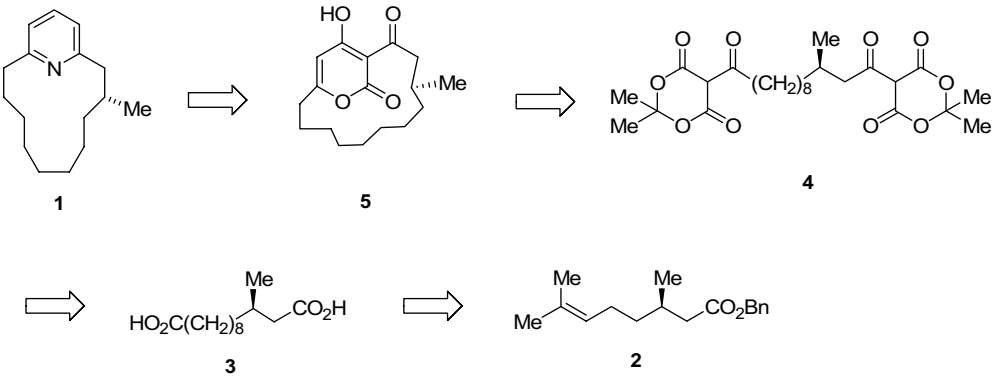
Ruzicka and Prelog[5] in 1946. Despite its rather simple structure, **1** is a fascinating and repeated target for a total synthesis.[6–8] In this study, we report an application of the ketene cycloaddition methodology to the highly efficient synthesis of compound **1**.

We envisaged the application of the ketene methodology to the synthesis of muscopyridine **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]

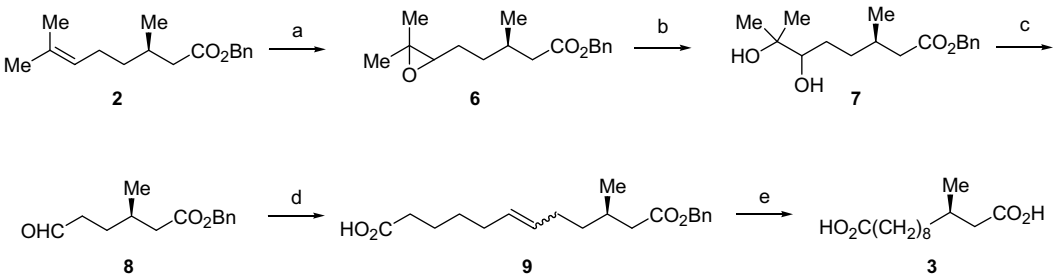
The synthesis of **3** was commenced with the epoxidation of the olefinic benzyl ester **2** with *m*-CPBA to provide epoxide **6** in 98% yield as a mixture of diastereomers (Scheme 3). The ring opening reaction of **6** to yield diol **7**, followed by the oxidative cleavage of **7** with $NaIO_4$, 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).

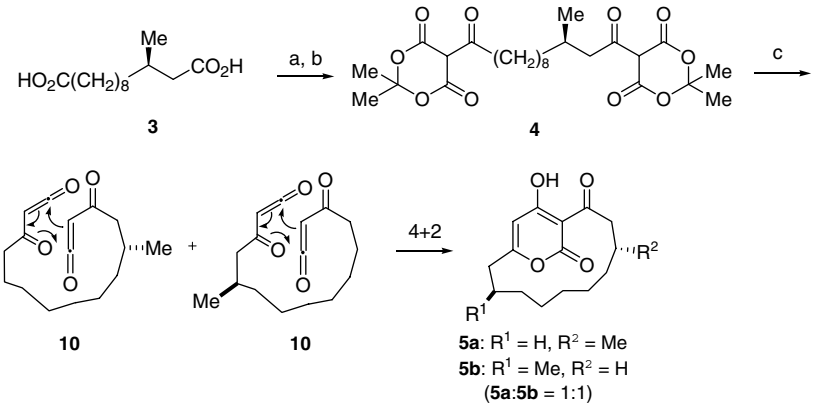
It has been reported that dehydroacetic acid is transformed into 2,6-dimethyl-4-pyrone on heating with concd HCl,[12,13] and the pyrone ring is converted into a pyridine ring by heating with ammonia.[12,14] We have applied this ring transformation to the synthesis of *meta*-pyridinophane from *para*-cyclophane.[4] 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



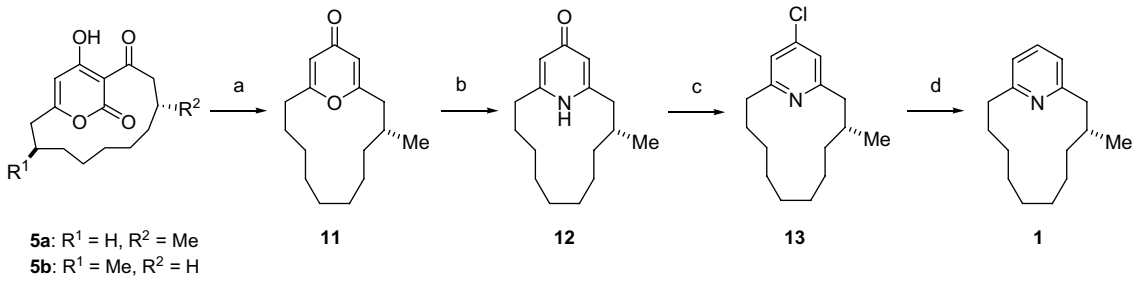
Scheme 2. Retrosynthesis of muscopyridine.



Scheme 3. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h then rt, 10 h, 98%; (b) H_2SO_4, Et_2O/H_2O, quant.; (c) $NaIO_4$, Et_2O/H_2O, rt, 1 h, quant.; (d) $BrPPh_3(CH_2)_5CO_2H$ (**10**), *t*-BuOK, THF, 0 °C, 1 h then rt, 30 h, 76%; (e) H_2, $Pd(OH)_2$, 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) H_2/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 muscopyridine[15] 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**: $[\alpha]_D^{23}$ +13.1 (*c* 0.50, $CHCl_3$), lit.,[5] $[\alpha]_D^{23}$ +17.4 (*c* 1.92, $CHCl_3$), lit.,[6a] $[\alpha]_D^{25}$ +13.3 (*c* 0.90, $CHCl_3$), lit.,[7b] $[\alpha]_D^{23}$ +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).