Intramolecular Michael Reaction using Trialkylsilyl Trifluoromethanesulfonates and Tertiary Amine System: Total Synthesis of (±)-Ricciocarpin A

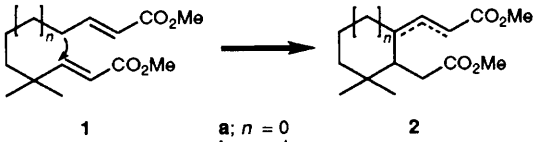
Masataka Ihara, Shuichi Suzuki, Nobuaki Taniguchi and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Intramolecular Michael reaction of bis-α,β-unsaturated esters **1** forming **2** was carried out by the action of a trialkylsilyl trifluoromethanesulfonate in the presence of a tertiary amine; the product was transformed into ricciocarpin A **8**.

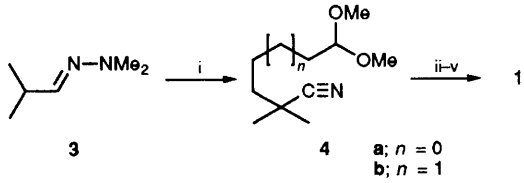
It is known that the intramolecular Michael reaction provides powerful methods for the construction of ring systems.[1] Recently, serial Michael reactions of diesters initiated by external Michael donors have been developed for creation of functionalised ring compounds.[2] As an extension of our research on intramolecular Michael reactions,[3] we studied an unprecedented cyclisation reaction of diesters **1** to **2** (Scheme 1). We report the achievement of this transformation by the use of a trialkylsilyl trifluoromethanesulfonate in the presence of a tertiary amine together with its application for a synthesis of (±)-ricciocarpin A **8**, a biologically important sesquiterpene.[4]

Substrates **1a** and **1b** for the key reaction were prepared starting from **3**. Alkylation of **3** accompanied with elimination[5] in the presence of lithium diisopropylamide (LDA) produced **4a** and **4b**, which were then converted into **1a** and **1b** in four steps (Scheme 2). Although the usual basic treatment of **1** gave poor results, the desired transformation was performed with a trialkylsilyl trifluoromethanesulfonate and a tertiary amine system.[3] The results are summarised in Table 1. It is noteworthy that bicyclic compounds **7a** and **7b**, formed presumably by a tandem Michael–Dieckmann reaction,[6] were



1 **a**; $n = 0$ **b**; $n = 1$ **2**

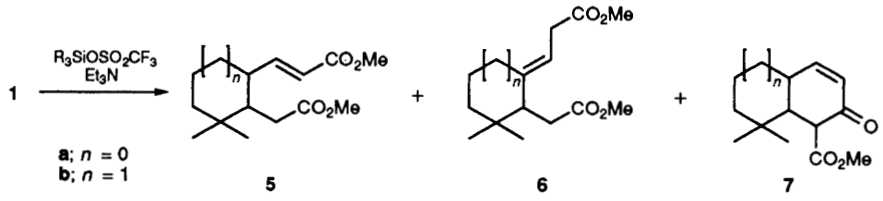
Scheme 1



3 **4** **a**; $n = 0$ **b**; $n = 1$

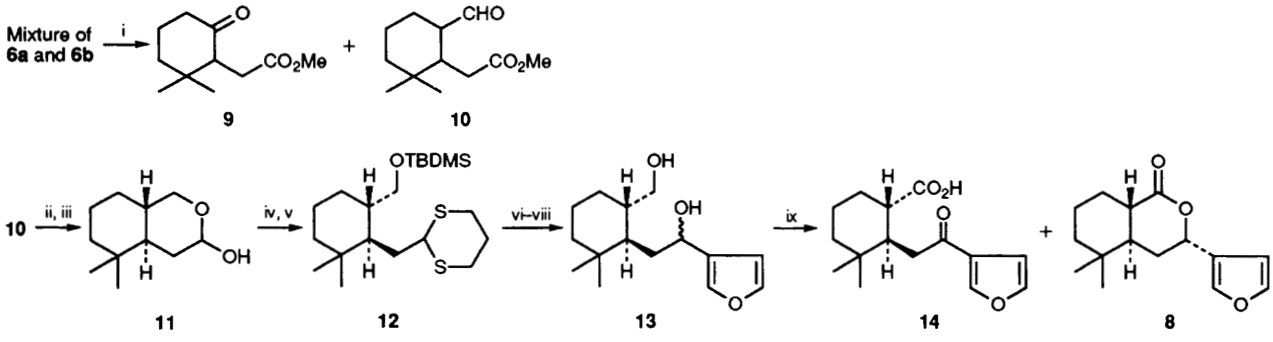
Scheme 2 *Reagents and conditions*: i, LDA, −78 °C; $Br[CH_2]_3[CH_2]_nCH(OMe)_2$, tetrahydrofuran (THF), 0 °C (n = 0, 76%; n = 1, 70%); ii, diisobutylaluminium hydride (DIBAH), CH_2Cl_2, −78 °C; silica gel (n = 0, 93%; n = 1, 92%); iii, NaH, $(MeO)_2POCH_2CO_2Me$, dimethoxyethane (DME) (n = 0, 83%; n = 1, 95%); iv, pyridinium toluene-*p*-sulfonate, H_2O–THF (1 : 1 v/v); v, $Ph_3P{=}CHCO_2Me$, MeCN (n = 0, 97%; n = 1, 99% for two steps)

Table 1 Treatment of **1** with trialkylsilyl trifluoromethanesulfonates in the presence of Et_3N[a]



Entry	Substrate	$R_3SiOSO_2CF_3$[b]	Yield (%) of **5** and **6** (ratio)[c]	Yield (%) of **7**[c]
1	**1a**	TBDMSOTf	53 (3 : 1)	12
2	**1a**	TMSOTf	81 (2 : 1)	0
3	**1b**	TBDMSOTf	89 (5 : 3)[d]	3.8
4	**1b**	TMSOTf	80 (1 : 1.7)[e]	0
5	**1b**	TIPSOTf	77 (8 : 5)[f]	0

[a] All reactions were carried out by use of 4 equiv. of $R_3SiOSO_2CF_3$ and 8 equiv. of Et_3N in CH_2Cl_2 at room temperature for 1–3 h and the reaction mixture was treated with acid. [b] *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf). [c] Products were isolated by column chromatography. [d] *trans*- and *cis*-Substituted **5b** were obtained in a 1.5 : 1 ratio. [e] Only *trans*-substituted **5b** was obtained. [f] After treatment with 10% aqueous $HClO_4$, *trans*- and *cis*-substituted **5** were obtained in *ca.* 1 : 1 ratio.



Scheme 3 *Reagents and conditions*: i, O_3, CH_2Cl_2, −78 °C; Et_3N (**9**, 27%; **10**, 44%); ii, DBU, CH_2Cl_2, 20 °C (78%); iii, $NaBH_4$, EtOH, −5 °C (99%); iv, $(HSCH_2)_2CH_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (97%); v, TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (100%); vi, MeI, $NaHCO_3$, H_2O–MeCN (1 : 8 v/v), 45 °C; vii, 3-bromofuran, Bu^nLi, THF, −78 °C; viii, Bu^n_4NF, THF, 0 °C (62% for three steps); ix, PDC, DMF, 3 days (**14**, 23%; **8**, 16%)

obtained as single stereoisomers by the reaction using TBDMSOTf–Et_3N.

Ricciocarpin A **8**, which was recently isolated from *Ricciocarpos natans*[4a] and exhibits potent molluscicidal activity,[4b,c] was synthesised using the above products. The mixture of **5a** and **5b**, obtained by the reaction in Entry 3, was ozonolysed to give **9** and **10** (Scheme 3). Equilibration of **10** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by reduction with $NaBH_4$, provided a 7 : 1 mixture of **11** and its *cis*-fused isomers. After transformation into **12**, deprotection of the dithioacetal group, followed by the addition of 3-furyllithium and desilylation afforded a 1.3 : 1 mixture of diols **13**. Oxidation of **13** with pyridinium dichromate (PDC) in dimethylformamide (DMF) produced the ketoacid **14**, m.p. 130–131 °C (lit.,[4d] m.p. 131–132 °C), along with (±)-ricciocarpin A **8**, m.p. 92–92.5 °C (lit.,[4d] m.p. 95–96 °C). Eicher and his coworkers have stereoselectively converted **14** into (±)-**8**.[4d] The spectral data of the synthetic **8** were consistent with those of the natural product.

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