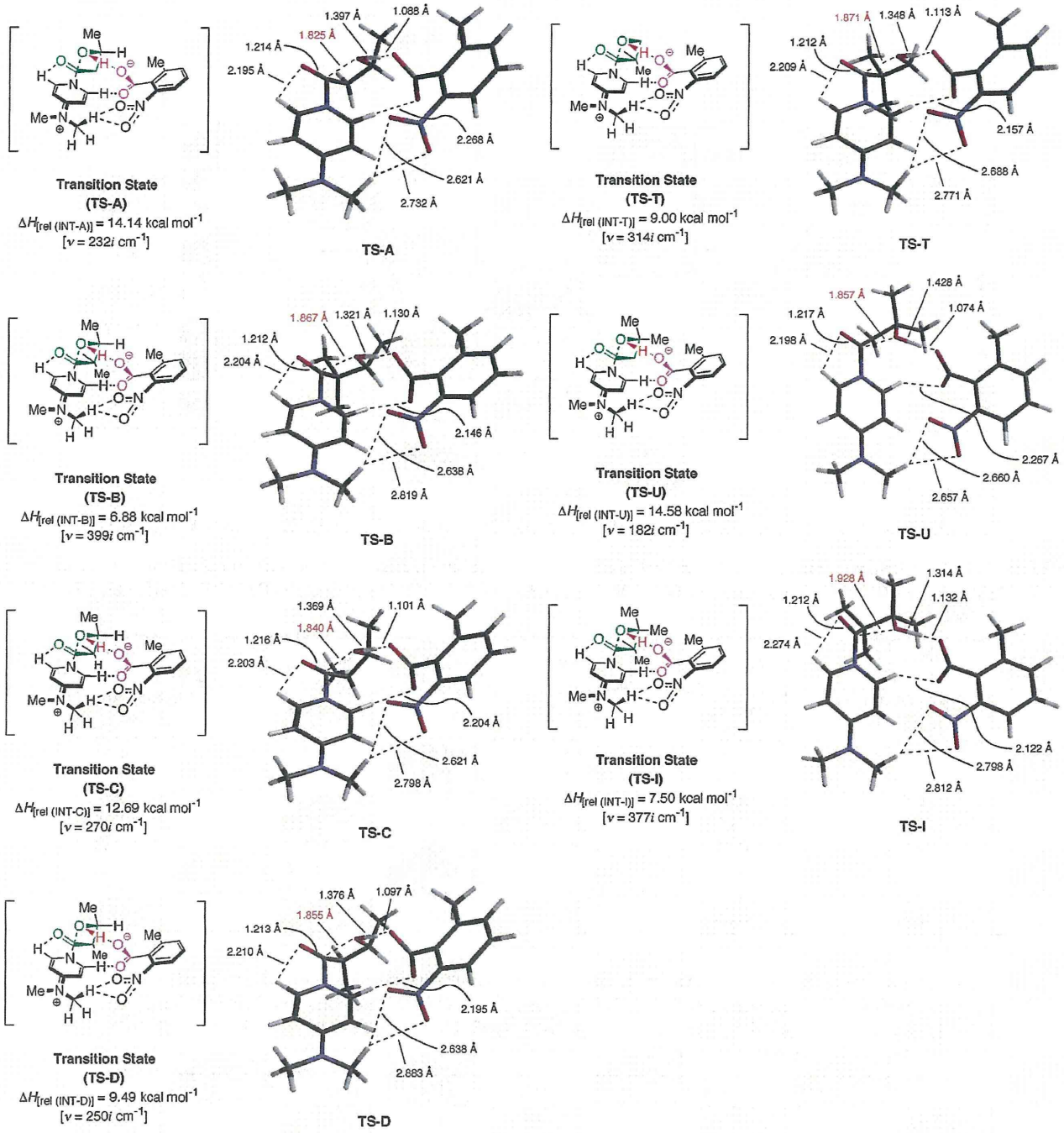
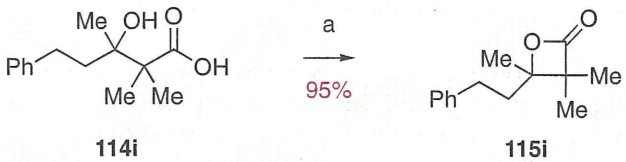


Figure 12. Three-dimensional transition structures (**TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I**) to form β-lactones (**2A–2D**, **2T**, **2U**, and **2I**) from 3-hydroxycarboxylic acids (**1A–1D**, **1T**, **1U**, and **1I**).



114i **115i**

Scheme 27. MNBA-mediated cyclization of β-hydroxycarboxylic acid **114i** to form β-lactone **115i**. *Reagents and conditions*: (a) MNBA, DMAP, Et_3N, CH_2Cl_2, rt.

ring closures of precursors, *trans*-2,3-disubstituted seco-acids **114d**, **114e**, and **126**, 2,2,3-trisubstituted seco-acid **114b**, and 2,2,3,3-tetrasubstituted seco-acid **114i**, were demonstrated to afford the corresponding *trans*-2,3-disubstituted β-lactones **115d**, **115e**, and **127**, 2,2,3-trisubstituted β-lactone **115b**, and 2,2,3,3-tetrasubstituted β-lactone **115i** in high yields (69%, 83%, 91%, 89%, and 95%, respectively). These experimental results were theoretically explained by a mechanistic study by using DFT calculations for the cyclization of the model seco-

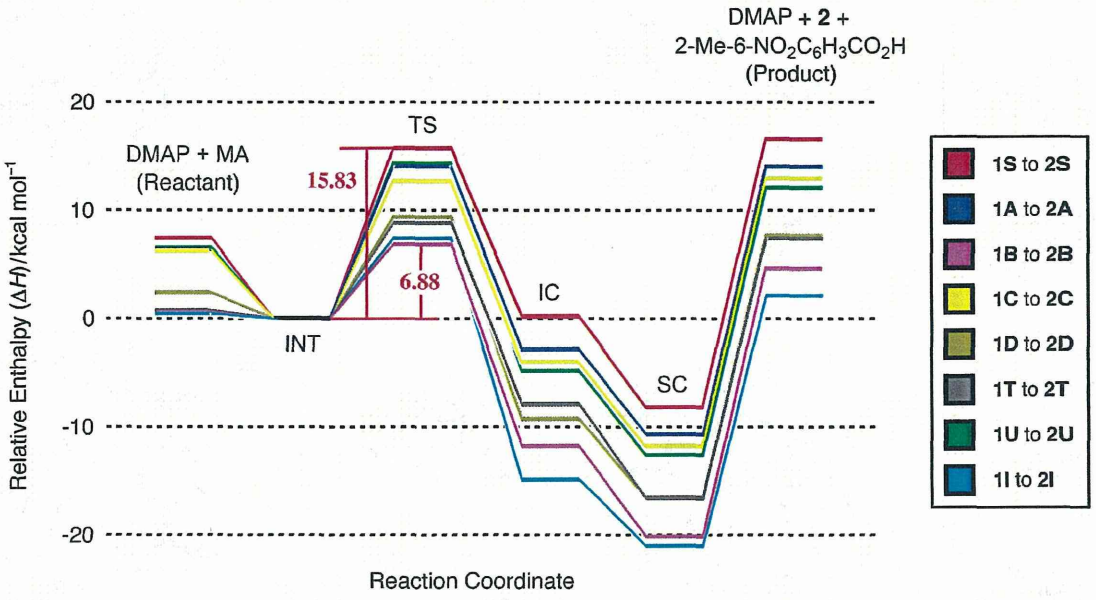


Chart 1. Reaction coordinates to form β-lactones (**2A–2D**, **2S–2U**, and **2I**) from 3-hydroxycarboxylic acids (**1A–1D**, **1S–1U**, and **1I**).

Table 9. Calculated Relative Enthalpies (ΔH) [in kcal mol^{-1}] of the Transition States and Intermediates for the Formation of Lactones **2A–2D**, **2S–2U**, and **2I** from 3-Hydroxycarboxylic Acids (**1A–1D**, **1S–1U**, and **1I**) at 298.15 K at the B3LYP/6-31G*//B3LYP/6-31G* Level of Theory

	DMAP + MA from **1A–1D**, **1S–1U**, **1I** (Reactant)	**INT-A–INT-D** **INT-S–INT-U** **INT-I**	**TS-A–TS-D** **TS-S–TS-U** **TS-I**	**IC-A–IC-D** **IC-S–IC-U** **IC-I**	**SC-A–SC-D** **SC-S–SC-U** **SC-I**	DMAP + **2A–2D**, **2S–2U**, **2I** + 2-Me-6-$NO_2C_6H_3CO_2H$ (Product)
S	7.64	0.00	15.83	0.32	−8.08	16.54
A	6.73	0.00	14.14	−2.77	−10.43	14.13
B	0.73	0.00	6.88	−11.65	−19.91	4.69
C	6.47	0.00	12.69	−3.79	−11.68	13.00
D	2.42	0.00	9.49	−9.09	−16.28	7.88
T	0.90	0.00	9.00	−7.90	−16.40	7.48
U	6.80	0.00	14.58	−4.85	−12.52	12.22
I	0.56	0.00	7.50	−14.61	−20.95	2.28

Table 10. Yields of Lactones **115a–115d**, and **115i**, and Calculated Relative Gibbs Free Energies (ΔG) [in kcal mol^{-1}], Enthalpies (ΔH) [in kcal mol^{-1}], and the Products of Entropies and Temperature ($T\Delta S$) [in kcal mol^{-1}] for the Transition States **TS-A–TS-D**, **TS-S–TS-U**, and **TS-I** at 298.15 K at the B3LYP/6-31G*//B3LYP/6-31G* Level of Theory

	115b	**115i**		**115d**	**115c**	**115a**		
Yield/%	89	95		69	13	5		
	TS-B	**TS-I**	**TS-T**	**TS-D**	**TS-C**	**TS-A**	**TS-U**	**TS-S**
ΔG	6.56	7.16	8.84	9.32	12.66	14.04	14.50	15.80
ΔH	6.88	7.50	9.00	9.49	12.69	14.14	14.58	15.83
$T\Delta S$	0.32	0.34	0.16	0.17	0.03	0.10	0.08	0.03

acids **1D**, **1B**, and **1I** to form β-lactones **2D**, **2B**, and **2I** through the low energy transition states **TS-D**, **TS-B**, and **TS-I**.

11. Conclusions

In this award account, we briefly outlined the development of the dehydration condensation reactions that have been studied in our laboratory. It was clarified that aromatic carboxylic anhydrides are stable and easy-to-handle compounds at room temperature and function as highly reactive coupling reagents in combination with an adequate catalyst. Using TFBA with a Lewis acid catalyst is one of the most powerful protocols for carbon–oxygen bond formation, enabling the synthesis of carboxylic esters and lactones in good yields. Furthermore, using MNBA with a nucleophilic catalyst, such as

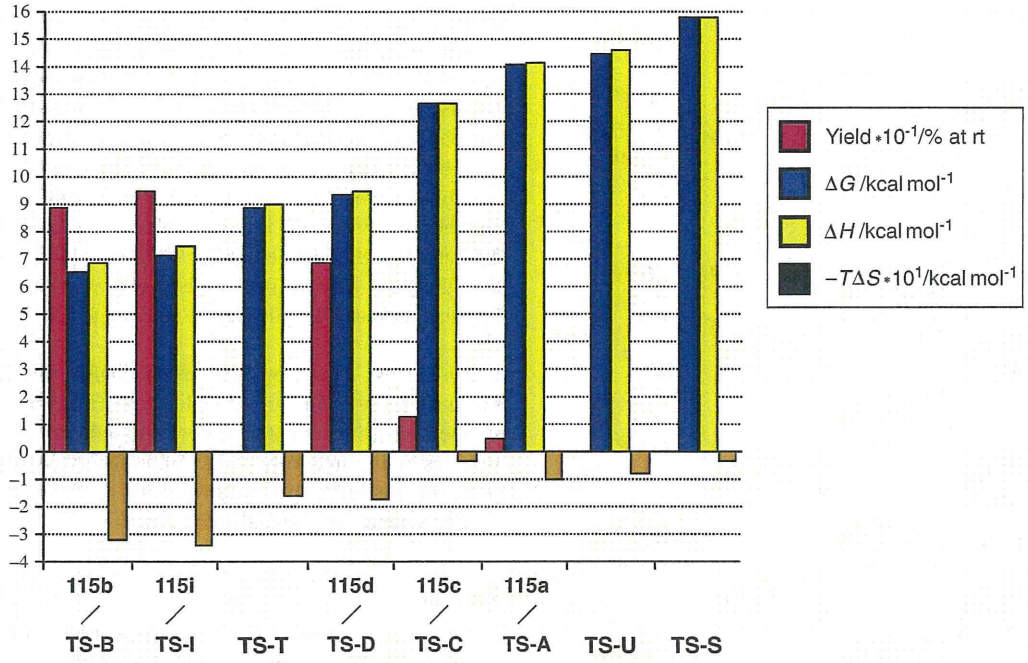
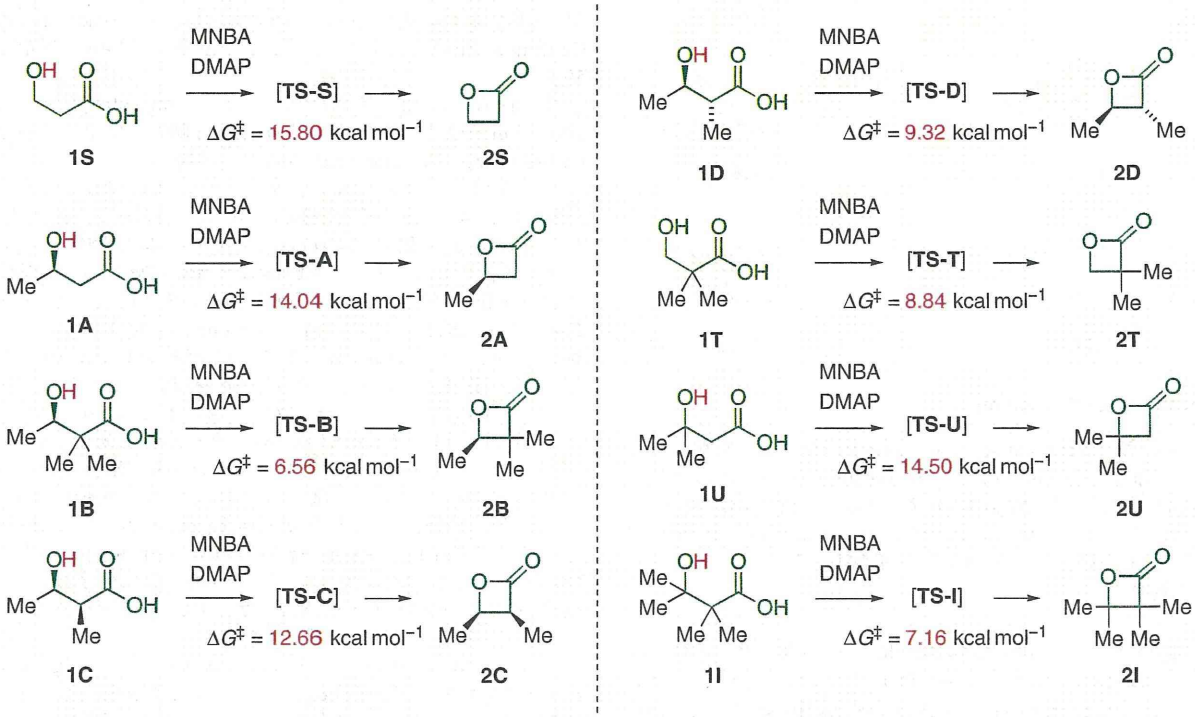
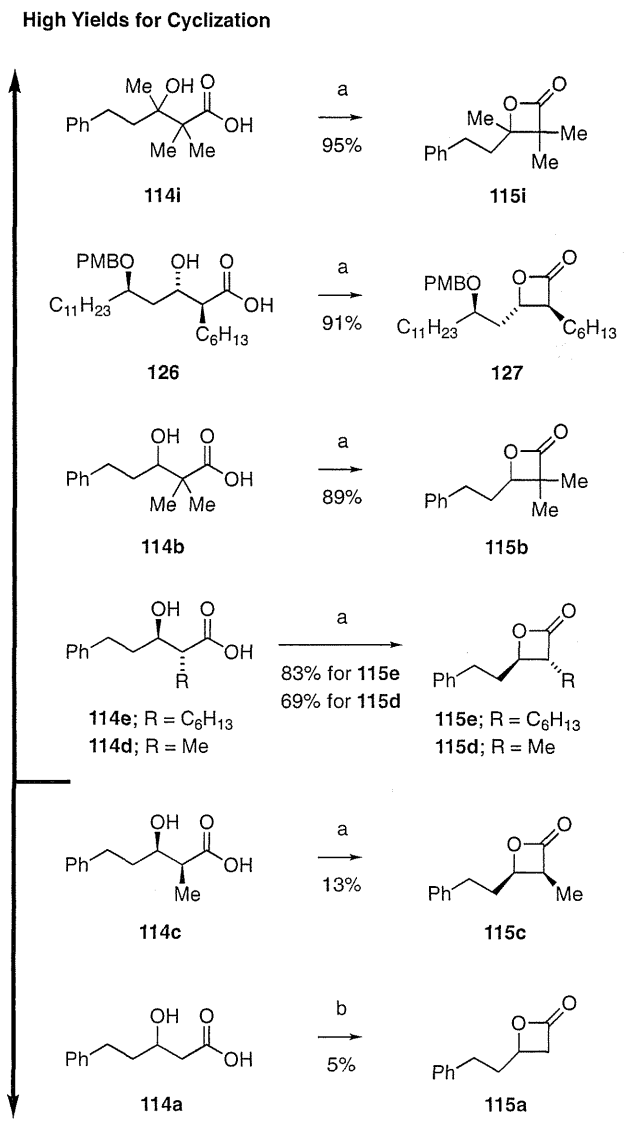


Chart 2. Comparison of yields of lactones **2a–2d** and **2i**, with thermodynamic potentials of the model lactonization to form (**2A–2D**, **2S–2U**, and **2I**) via the transition states **TS-A–TS-D**, **TS-S–TS-U**, and **TS-I**.



Scheme 28. Calculated transition Gibbs free energies ($\Delta G^{\ddagger}$) of the model reactions for the formation of β-lactones (**2S**, **2A–2D**, **2T**, **2U**, and **2I**) starting from 3-hydroxycarboxylic acids (**1S**, **1A–1D**, **1T**, **1U**, and **1I**) via transition structures (**TS-S**, **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I**).

DMAP or DMAPO, under basic conditions enables convenient preparation of acid-sensitive carboxylic esters, lactones, and amides. It is notable that the experimental procedure for the dehydration condensation reaction using substituted benzoic anhydrides is quite simple, and nearly pure products are facilely obtained. To demonstrate the utility and versatility of this lactonization reaction, we presented the total syntheses of (−)-cephalosporolide D ((−)-**3**), (−)-octalactin A ((−)-**4**), (−)-octalactin B ((−)-**25**), 2-epibotcinolide (**49**), (−)- and (+)-2-hydroxytetracosanolides ((−)-**77** and (+)-**77**), (−)- and



Scheme 29. Classification based upon yields of the MNBA-mediated cyclization of β-hydroxycarboxylic acids **114a–114e**, **114i**, and **126** to form β-lactones **115a–115e**, **115i**, and **127**. *Reagents and conditions*: (a) MNBA, DMAP, Et_3N, CH_2Cl_2, rt; (b) MNBA, DMAP, Et_3N, CH_2Cl_2/THF, rt.

(+)-2-hydroxy-24-oxooctacosanolides ((−)-**78** and (+)-**78**), and (−)-tetrahydrolipstatin ((−)-THL, (−)-**117**), and the semi-synthesis of the erythromycin A skeletons **103b**, **103c**, **104c**, and **105b**, all of which were performed in our laboratory. Transition structures **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I** were also identified as being involved in the formation of the β-lactones **2A–2D**, **2T**, **2U**, and **2I** from the 3-hydroxycarboxylic acids **1A–1D**, **1T**, **1U**, and **1I**, respectively, using DFT calculations, and the reactivity of the seco-acids **1A–1D**, **1T**, **1U**, and **1I** were successfully predicted on the basis of the calculated thermodynamic properties of the respective transition structures **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I**. Many other research groups have also applied and evaluated MNBA-promoted organic transformations for the preparation of various key intermediates in the total syntheses of other natural products. Furthermore, this protocol can now be utilized as a general and powerful method for the construction of not only natural products but also highly modified multifunctionalized artificial compounds. We hope that the advances made to date in the synthetic methodology for the formation of large-, medium-, and small-sized lactones will certainly contribute to future distinguished and fruitful chemical syntheses of natural products and useful biologically active agents.

The author expresses his hearty thanks for the valuable efforts of former and current colleagues who contributed to the research on using aromatic carboxylic anhydrides. Our investigations in this area were partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Isamu Shiina was born in Tokyo, Japan, in 1967. He completed his B.Sc. and M.Sc. in the Department of Applied Chemistry, Faculty of Science, Tokyo University of Science (TUS), and he joined the Research Institute for Science and Technology of TUS as an Assistant Professor in the research group of Professor T. Mukaiyama in 1992. After receiving his Ph.D. from the University of Tokyo (UT) under the supervision of Professor K. Narasaka in 1997, he was promoted to Lecturer at the TUS. He started his independent laboratory in the Department of Applied Chemistry, Faculty of Science, TUS, as a Lecturer in 1999 and then he was promoted to Associate Professor (2003) and a Full Professor (2008). He has received the Chemical Society of Japan Award for Young Chemists (1997), The Fujisawa Foundation Award (2002), Kurata Memorial Foundation Award (2004), Banyu Young Chemist Award (2006), Toray Science Foundation Award (2009), The Naito Foundation Award (2010), and the Chemical Society of Japan Award for Creative Work (2012). His research interests include the development of useful synthetic methods, especially for asymmetric synthesis and cyclization methodologies, and the total synthesis of complex natural products and biologically important molecules.