計劃名稱：生物鹼合成

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執行單位：國立交通大學應用化學研究所

一、 中文摘要

(1) 喜樹鹼合成研究

(2) Lentiginosine 合成研究

(3) 毒扁豆鹼合成研究

(4) Tacamonine 合成研究

(5) Tangutorine 合成研究

關鍵詞：生物鹼、合成策略

Abstract:

(1) Synthetic studies on camptothecin

(2) Synthetic studies on Lentiginosine

(3) Synthetic studies on physostigmine

(4) Synthetic studies on Tacamonine

(5) Synthetic studies on Tangutorine

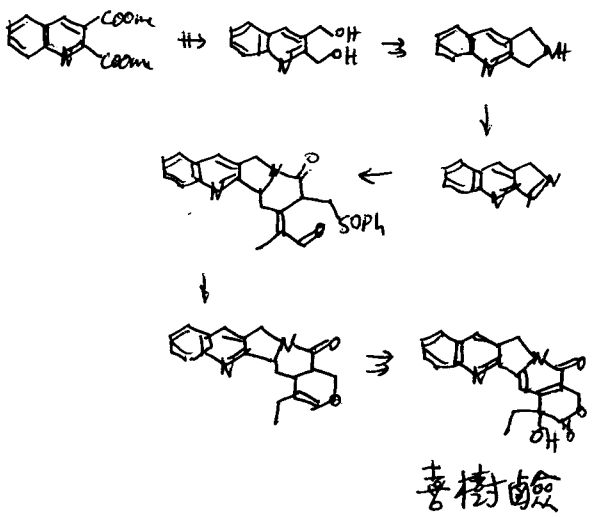
Keywords: alkaloids, synthetic strategies

二、 目的與結果

本計劃以生物鹼合成爲經，探討策略爲緯，藉以訓練學生之思考和技術。多個計劃均是初步探索，以確定後續之方向和取捨。本年度之進展情形分述如下：

(1) 喜樹鹼合成

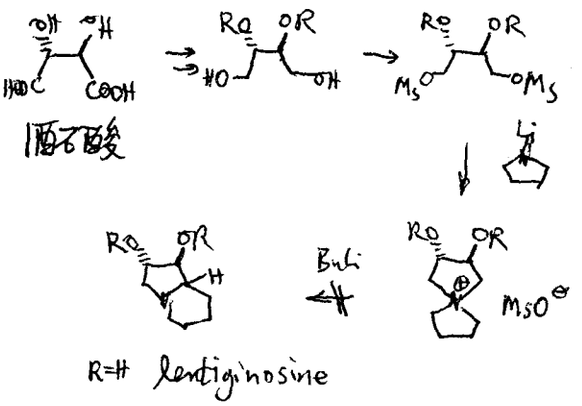
因爲這個化合物具抗癌作用，爲藥物學家和化學家重視。我們希望發展簡短合成途徑完成。即如下圖所示：



不幸的是，起始物之吡咯併喹啉按照一組印度人(Yadav 等)，發表的方法去建構時，完全失敗。報導高產率之反應，實不可行，而且產物十分複雜。雖或可重新考慮設計另一些合成法，但因人手不足，從事該工作的人又進行別的實驗，故此計劃暫擱置。

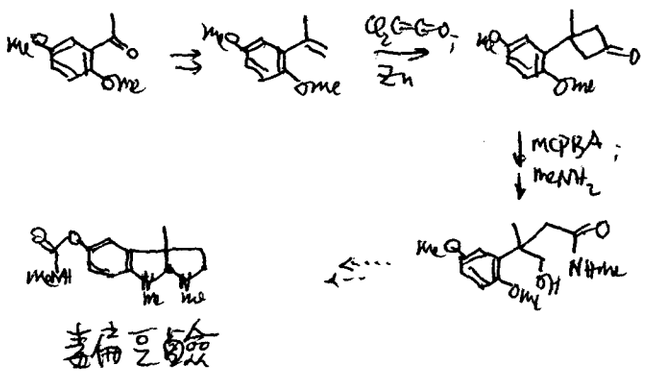
(2) Lentiginosine 合成

計劃從酒石酸開始，經酯化，又保護了二級 OH 然後還原酯，一級醇改爲磺酸基，再與吡咯啶反應，意欲促進重排，但多次嘗試失敗。



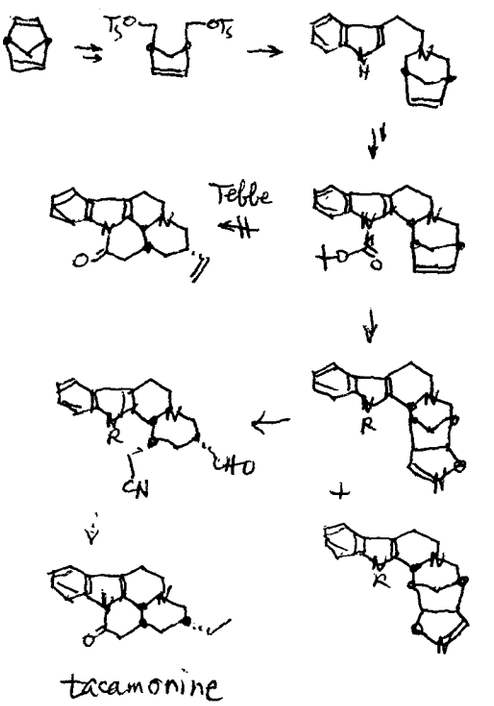
(3) 毒扁豆鹼合成

合成策略以建立環丁酮，再擴環爲基礎，如圖示，具有適當官能基的醯胺中間體已得到。但因責任學生沒有好好做下去，計劃仍是停留在此階段。



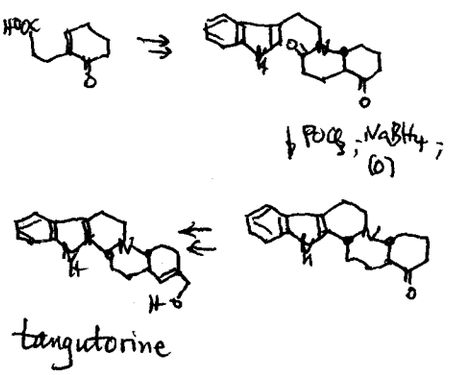
(4) Tacamonine 合成

此計劃幾度變更(但已有兩相關論文發表)爲了發展一條可控制立體化學之路線，以氧化還原手續把 C 環閉合，其後橋環之切割，可以用 1,3-二極環合加成後，再行開裂而完成。不過此法仍有改進空間。



(5) Tangutorine 合成

如圖示進行，只是閉合 C 環的產率不佳，下年度繼續研究。



第224届美国化学会年会

此会在2002.8.18-22在波士顿举行。一如以往，参加人数极众。有机化学有关的论文800多篇，目不暇给。此次主题很多，计有核酸基础之医药，光化学，新反应与新方法，固相及组合合成，金属催化，不对称合成，复杂化合物合成，生物有机，分子识辨和自组，更有特别研讨会纪念Cram教授的，邀请了Breslow，Diederich，Stoddart，Stang等多人作专题演讲。又有新合成试剂组是庆祝Brown教授九十岁的，除他的学生如Negishi等外，还请到Trost，Smith等人。四面体的原创奖也在大会中颁发。今年得奖为哈佛大学的日裔岸义人教授。除了本人作得奖演说外，Schreiber，Reetz…等为陪衬。Schreiber去年得此，今年讲化学遗传，可说万人空巷，听众上千人。另一重要的Cope奖之得主有Williams，Johnson，Katritzky，Panek，Shair，Joullie，Shibasaki，Zhang，Fürstner，最后是Grubbs。可说一时俊彦云集。中国人（大陆）在美国的张绪穆也是学者，谈述他的不对称合成配位体工具，相当精彩。

其他重要有机化学专家受重视的演讲包括哥伦比亚大学的Danishefsky教授，哈佛大学的Jacobsen教授，内容详实，没有令人失望。

在本人所听讲的论文中，饶有启发性的有由Polaroid公司研究人员发表的感热生色染料加热时发生偶合反应，可望成为新的产品。MIT有侦测神经毒气的文章，是藉着一个化学反应形成强烈萤光剂而成功的。新的导电聚合物采用calix[4]arene骨架的氧醌，使电子跳跃其间而发挥功能，十分新颖。又有研究摺叠蛋白质β-串结构及性质，主链引进了一个六员杂环烯酮，使构型具有固定的β-肽酸状态，维持链与链之间氢键。

美国化学会在展览场地举办了化学的论文最多引用奖，颁给哈佛大学柯雷教授。本人曾与他有师徒关系，故趋前庆贺及叙旧，相谈甚欢。为此会参加的另一收获。

ORGN

771.
SYNTHESIS OF DINITROPHENOL ORTHO-PHOSPHATES AND SULFATES FROM SANGER'S REAGENT AND THE CORRESPONDING PEROXYMONOANION.
Edward J. Behrman, and Ssuhen Chen, Department of Biochemistry, Ohio State University, 484 W. 12th Ave., Columbus, OH 43210, Fax: 614-292-6773, Behrman.1@osu.edu

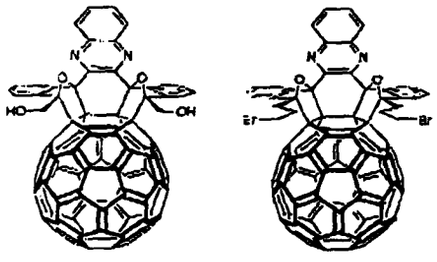
Peroxymonophosphate and peroxymonosulfate anions react with 2,4-dinitrofluorobenzene under very mild conditions to give the title compounds.Attack by the peroxyanion and expulsion of the fluoride ion yields the arylperoxysulfate or phosphate which then rearranges to the phenol ortho-sulfate or phosphate. We are exploring this reaction with other alpha nucleophiles and electrophiles.

772.
SYNTHETIC APPROACH TO TANGUTORINE. *Tse-Lok Ho, Dept. of Applied Chemistry, National Chiao Tung University, 1001 Tasueh Rd., Hsinchu, Taiwan, Fax: 886-35-723764, tlho@cc.nctu.edu.tw and Eugueni Gorobets, Dept. of Applied Chemistry, National Chiao Tung Univ*

The pentacyclic indole alkaloid tangutorine was isolated from a plant from northwestern China. We have initiated a synthetic study from tryptamine and 3-(6-oxocyclohex-1-enyl)propionic acid. Two cyclization steps were achieved before functionalization of the E-ring.

773.
SYNTHETIC [2+2+2] APPROACH FOR OPENING THE [60]FULLERENE CAGE.
Shih-Ching Chuang, Michael Sander, Thibaut Jarrosson, and Yves Rubin, Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Ave, Los Angeles, CA 90095-1569, schuang@chem.ucla.edu

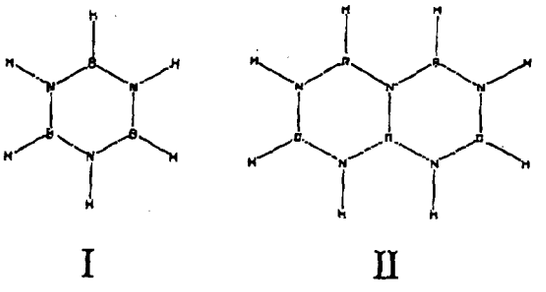
The synthesis of [60]fullerene derivatives with openings in the carbon framework and the subsequent insertion of atoms into the C60 core is of great interest because of the anticipated physical properties these compounds would have. The approach used to open C60 is proposed to follow a [2+2+2] ring-opening mechanism. Two candidate molecules were designed and synthesized. Bisadducts 1 and 2 have radical generating centers for addition to the last C=C bond of the functionalized 6-membered ring. Opening reactions of these and other C60 molecules will be described.



1 2

774.
BORON-NITROGEN ANALOGUES OF BENZENE AND NAPHTHALENE: PRECURSORS TO BN FULLERENES?.
N. R. Conley, and J. J. Lagowski, Department of Chemistry and Biochemistry, The University of Texas at Austin, 105 E. 24th St., Welch Hall, Austin, TX 78712, Fax: 512-471-3288, Lagarto2@aol.com

We have previously reported the formation of [60]- and [70]-fullerene by (a) incomplete combustion of benzene and (b) pyrolysis of naphthalene or 1-bromonaphthalene. Here we investigate the combustion and pyrolysis of the boron-nitrogen analogues of benzene (I) and naphthalene (II), respectively, to determine if they are potential precursors to BN fullerenes. MNDO calculations suggest that the stability of B3ON3O approximates that of C60, although its chemical properties are expected to be significantly different.

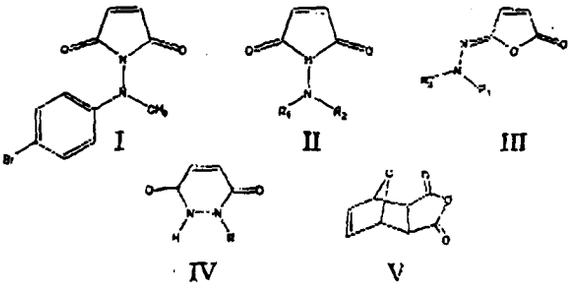


I II

775.
SYNTHESIS AND CHARACTERIZATION OF N-(4-BROMOPHENYL)-N-METHYLAMINOMALEIMIDE.
Nicholas R. Conley, Department of Chemistry and Biochemistry, The University of Texas at Austin, 105 E. 24th St., Austin, TX 78712, Lagarto2@aol.com, and C. Grant Willson, Department of Chemistry, University of Texas at Austin

N-(4-bromophenyl)-N-methylaminomaleimide (I) is a valuable intermediate in the synthetic route to the key monomers that will be used to prepare new, thermally stable polymers with high second order nonlinear optical coefficients. Synthesis of N-substituted aminomaleimides (II) is neither trivial nor well documented. Two stable constitutional isomers of II—aminoisomaleimide (III) and pyridazinedione (IV)—can be produced from the same precursors under varied reaction conditions. Consequently, a staggering number of papers appeared in the literature as late as 1980 in which III and IV were mischaracterized as II. To date, no general synthetic method has been reported for the preparation of II. We synthesized I in good yield by condensation of the exo-furan/maleic anhydride Diels-Alder adduct (V) and N-methyl-N-phenylhydrazine, followed by removal of furan by the retro Diels-Alder reaction. Selective bromination in the para position was effected with N-bromosuccinimide in the presence of silica gel in carbon tetrachloride. The structure of I was confirmed unambiguously by x-ray crystallography and other spectroscopic techniques. We have demonstrated that this method is a general route to other derivatives of II.

776.
SYNTHETIC STUDIES TOWARDS RAPAMYCIN: C10-C27 FRAGMENT SYNTHESIS BY SILICON-MEDIATED FRAGMENTATION.
Philip Parsons[1], Dave Cheshire[2], and Kyungsoo Oh[1]. (1) Chemistry, Physics and Environmental Science, Sussex University, Falmer, Brighton BN1 9QJ, United Kingdom, Fax: +44 1273 677 196, P.J.Parsons@susx.ac.uk, k.s.oh@sussex.ac.uk. (2) Department of Medicinal Chemistry, AstraZeneca Pharmaceuticals



I II III IV V

Efforts directed towards the synthesis of C10-C27 fragment of rapamycin (1) by a silicon-mediated fragmentation will be discussed. The extensive use of epoxide opening protocols is one of our unique features of the current study.

777.
TOTAL SYNTHESIS OF VELAMONE, A TRANS-CLERODANE DITERPENE.
Kazuya Ujihara[1], Hidenori Watanabe[2], and Takeshi Kitahara[2]. (1) Agricultural Chemicals Research Laboratory, Sumitomo Chemical Co., Ltd, 4-2-1, Takatsukasa, Takarazuka 665-8555, Japan, Fax: 0797-74-2129, ujihara@sc.sumitomo-chem.co.jp. (2) Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo

Velamone (1), a *trans*-clerodane diterpene, was isolated as one of the major constituents from the roots of the resource of Brazilian folk medicine, *Croton*

Pergamon

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TETRAHEDRON LETTERS

Abnormal and regioselective Wacker oxidation of 1,5-dienes

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Received 13 May 2003; revised 18 June 2003; accepted 30 June 2003

Abstract—The presence of an additional double bond can change the regioselectivity of the Wacker oxidation of a 1-alkene moiety to give the aldehyde product.

The Wacker oxidation[1] of 1-alkenes (except ethene) leads selectively to methyl ketones.[2] We were interested in reversing this regioselectivity which seems to originate from palladiohydroxylation of the alkenes in the Markovnikov sense to afford organometallic species that subsequently undergo dehydropalladation.[3] Reversal of the regioselectivity has been observed in alkene systems by means of heteroatoms[4–7] which probably coordinate with palladium intermediates. In our study we considered π-complexation instead of the previously known participation of n-donors. Here we report the successful intervention in cases of certain dienes.

Diene **1a** was prepared from *p*-methylisobutyrophenone by allylation, Grignard reaction with MeMgI and dehydration ($KHSO_4$), whereas **1b** was obtained from methyl 2,2-dimethyl-4-pentenoate, also by Grignard reaction and dehydration. To procure **1c** starting from 2,2-dimethyl-4-pentenal the Grignard reaction, PCC oxidation and Wittig reaction sequence was employed. When submitted to conventional Wacker oxidation conditions ($PdCl_2$, CuCl, O_2, DMF–H_2O) only the aldehydes **2a**, **2b**, and **2c** were generated in 73, 99, and 75% yields, respectively. We have not been able to detect any methyl ketones by NMR spectroscopy. Analogously, diene **3** also followed the same reaction pattern, furnishing **4** in 60% yield. Contrarily, alkenol **5** *gave a normal product* **6** *which was shown to be a* tautomeric mixture of the methyl ketone and the cyclic lactol.

In our opinion, the formation of **2a**, **2b**, **2c**, and **4** may be due to participation of the disubstituted double bond, such that unsymmetrical intermediates **A** appeared and then captured by water. The next intermediates **B** then underwent elimination of the [H-PdL_n] species. In normal circumstances the π-complexes of Pd are attacked in the alternative manner, resulting in palladiohydroxylation according to the Markovnikov Rule. It should be noted that **A** has a similar structure as that proposed for the Pd-catalyzed Cope rearrangement.[8] The major difference in its fate is perhaps the crucial presence of water that tends to intercept it. On the other hand, in the reaction of **5** a 5-*exo*-*trig* process was involved.

Diene **8** is a structural variant of **3**. The intermediate involving both double bonds resembles necessarily a bridged-ring system wherein the complexed double bonds are axially oriented. We observed the formation of an aldehyde from reaction at the methylene moiety, albeit **9** was isolated in only 19% yield. The result was due to partial decomposition during chromatographic purification and also probably reflects a higher strain and therefore less favorable reaction. Absence of oxidation at the vinyl substituent may also indicate the importance of steric factors. Interestingly, the active Wacker oxidation catalyst is supposed to be a polymeric Pd-Cu-DMF complex with a Pd:Cu stoichiometry of 2:1, in which the two different metal centers are linked by a chlorine atom (apical to Cu), while the Cu center is also coordinated by four DMF molecules.[9]

We also believed that the π-participation did not turn into a σ-bonding event. Otherwise aldehydes with a tetrasubstituted double bond (e.g. **7**) would have appeared. This latter scenario is dominant in the Pd-mediated Cope rearrangement.[8]

In conclusion, we have observed a change in the regioselectivity in the polar addition of 1-alkenes from the Markovnikov sense to an anti-Markovnikov fash-

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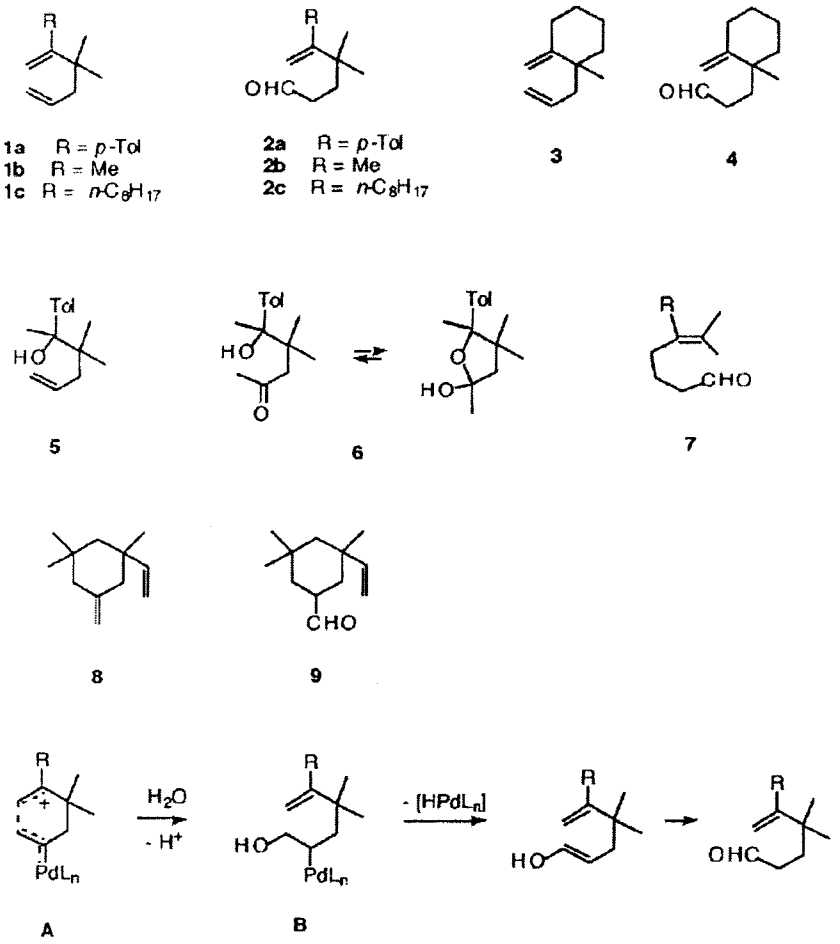

ion, when another double bond is judiciously placed in the same molecule. The through-space interaction[10] of two double bonds seems unique for such a phenomenon. On the other hand, n-donors actually accentuate the normal course of addition as shown in the case of **5**. A previous observation that an acrylamide underwent transformation into the β,β-dimethoxypropanamide derivative[11] is electronically biased, therefore quite different from that of ours. The unusual behavior of certain *N*-acylallylamines has been attributed to the coordination of palladium atom by the carbonyl group which led to the formation of *N*-acylaminopropanals.[12]

A representative example of the Wacker oxidation folllows: Preparation of **2a**: A mixture of **1a** (0.42 g, 2.1 mmol), $PdCl_2$ (0.08 g, 1.1 mmol), and CuCl (0.21 g, 2.1 mmol) in DMF (1 mL) and water (0.1 mL) was stirred under an oxygen atmosphere for 24 h at room temperature. It was diluted with dichloromethane, washed with water, dried over anhydrous Na_2SO_4, and concentrated in a rotary evaporator. The residual oil was chromatographed over silica gel [eluent:hexane:AcOEt 10:1] to afford **2a** (0.33 g, 72.8%). ν (C=O) 1725 cm^{-1}. H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.56 (t, $J=7.0$ Hz, 2H), 2.20 (s, 3H), 2.33 (t, $J=7.0$ Hz, 2H), 4.78 (s, 1H), 5.01 (s, 1H), 6.86 (d, $J=8.1$ Hz, 2H), 6.94 (d, $J=8.1$ Hz, 2H), 9.59 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (q), 27.4 (q), 32.1 (t), 38.5 (s), 39.8 (t), 114.0 (t), 128.0 (d), 128.3 (d), 135.7 (s), 139.6 (s), 156.4 (s), 201.5 (d). HRMS *m/z* 216.1517 (calcd for $C_{15}H_{20}O$ 216.1515).

Acknowledgements

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References

1. Tsuji, J. *Synthesis* **1984**, 369–384.
2. Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *17*, 2975–2976.
3. Backvall, J.-E.; Akermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411–2416.
4. Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955–5958.
5. Lai, J.-Y.; Shi, Shi, X.-x.; Dai, L.-x. *J. Org. Chem.* **1992**, *57*, 3485–3487.
6. Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758–1764.
7. Kang, S.-K.; Jung, K.-Y.; Chung, J. U.; Namkoong, E. Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678–4679.

L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*.

, T.; Nomura, T; Murahashi, S.-I. *J.* *Chem.* **1998**, *551*, 387–389.

, R. *Acc. Chem. Res.* **1971**, *4*, 1–9.

11. Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159–6167.
12. Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S.-I. *Chem. Commun.* **1991**, 1559–1560.