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Synthetic Studies toward GKK1032s, Novel Antibiotic Antitumor Agents: Enantioselective Synthesis of the Fully Elaborated Tricyclic Core via an Intramolecular Diels−Alder Cycloaddition

Moriteru Asano,[†] Munenori Inoue,*[,†,‡] Kazuhiro Watanabe,[§] Hideki Abe,[§] and Tadashi Katoh*[,§]

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan, Sagami Chemical Research Center, Hayakawa 2743-1, Ayase, Kanagawa 252-1193, Japan, and Department of Chemical Pharmaceutical Science, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

katoh@tohoku-pharm.ac.jp

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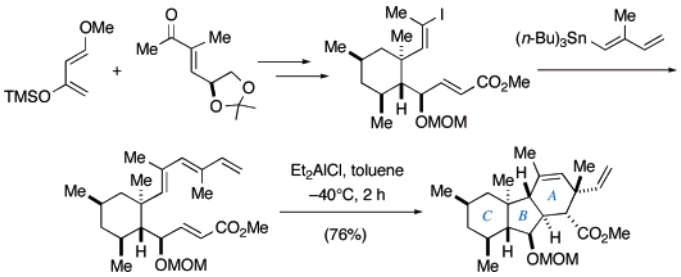

An enantioselective synthesis of the fully elaborated tricyclic decahydrofluorene core (ABC-ring system) of GKK1032s, novel antimicrobial and antitumor agents, has been accomplished for the first time by employing a highly diastereoselective intramolecular Diels−Alder (IMDA) reaction. The key substrate for the IMDA reaction was efficiently prepared through (i) an intermolecular Diels−Alder reaction between a siloxydiene and an optically active enone derived from D-mannitol to construct the appropriately functionalized C-ring and (ii) CuCl-promoted Stille coupling of an (*E*)-vinyl iodide and a vinylstannane to install the requisite triene side chain as the crucial steps.

Introduction

GKK1032A$_1$ (**1**), A$_2$ (**2**), and B (**3**) were isolated in 2001 by the Kyowa Hakko research group from the culture broth of *Penicillium* sp. GKK1032 (Figure 1).[1] The GKK1032s exhibit antitumor activity against the human cervical cancer-derived HeLaS3 cells, as well as antimicrobial activity against *Bacillus subtilis* no. 10707.[1] In 2002, Ōmura and co-workers also reported the isolation of a novel antimicrobial agent FO-7711CD6 from the culture broth of *Penicillium* sp.,[2] whose planar structure was incidentally identical to that of GKK1032A$_2$ (**2**). Subsequently, He and co-workers reported the isolation of pyrrocidines A (**4**) and B (**5**) from the fermentation broth of a fungus, *LL*-Cyan426, as antimicrobial agents against Gram-positive bacteria including drug-resistant strains and their structures were assigned as 3,6-bis-*epi*-3-demethyl analogues.[3] More recently, Isaka and co-workers reported the isolation of structurally related antituberculous agents, hirsutellones A−E from the insect pathogenic fungus *Hirustella nivea* BCC 2594 and hirsutellone F from the seed fungus *Trichoderma* sp. BCC 7579.[4]

The gross structure and relative stereochemistry of these natural products were determined by extensive spectroscopic studies including 2D NMR experiments (COSY, HMBC,

[†] Tokyo Institute of Technology.
[‡] Sagami Chemical Research Center.
[§] Tohoku Pharmaceutical University.

(1) (a) Koizumi, F.; Hasegawa, A.; Ando, K.; Ogawa, T.; Hara, M.; Yoshida, M. Jpn. Kokai Tokkyo Koho JP 2001247574, **2001**; *Chem. Abstr.* **2001**, *135*, 209979. (b) Hasegawa, A.; Koizumi, F.; Takahashi, Y.; Ando, K.; Ogawa, T.; Hara, M.; Yoshida, M. *43rd Symposium on the Chemistry of Natural Products*, Symposium Paper; Osaka, Japan, 2001, 467.

(2) Ōmura, S.; Komiyama, K.; Hayashi, M.; Masuma, R.; Fukami, A. Jpn. Kokai Tokkyo Koho JP 2002255969, 2002; *Chem. Abstr.* **2002**, *137*, 231476.

(3) He, H.; Yang, H. Y.; Bigelis, R.; Solum, E. H.; Greenstein, M.; Carter, G. T. *Tetrahedron Lett.* **2002**, *43*, 1633.

(4) (a) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577. (b) Isaka, M.; Prathumpai, W.; Wongsa, P.; Tanticharoen, M. *Org. Lett.* **2006**, *8*, 2815.

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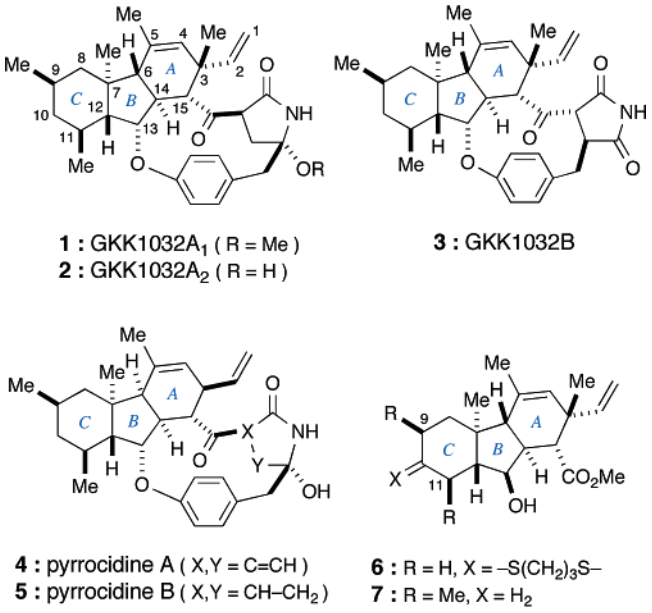
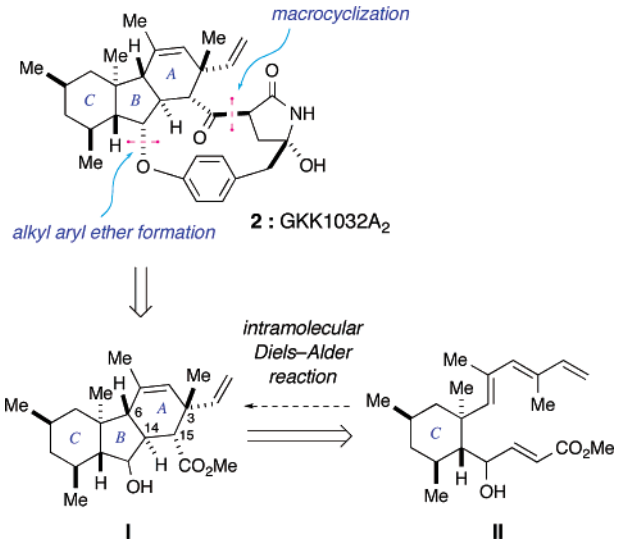


FIGURE 1. Structures of GKK1032A$_1$ (**1**), A$_2$ (**2**), and B (**3**); pyrrocidines A (**4**) and B (**5**); and decahydrofluorenes **6** and **7**.

NOESY, and ROESY spectra) and X-ray crystallographic analysis,[1−4] whereas their absolute configurations have not been revealed to date. Structural features of note include (i) an unprecedented tricyclic decahydrofluorene core (ABC-ring) and (ii) 12- or 13-membered macrocycles containing a δ-lactam or succinimide ring and *para*-substituted phenyl ether moiety. In 2003, Oikawa reported that the unique backbone of GKK1032A$_2$ (**2**) is biosynthetically constructed from L-tyrosine and a nonaketide chain flanked with five methyl groups probably by a polyketide synthase and a nonribosomal peptide synthetase hybrid.[5]

The quite unique structural features and attractive biological properties have made the GKK1032s and their related natural products exceptionally intriguing and timely targets for total synthesis. Synthetic studies toward these architecturally complex natural products have been presented by several research groups;[6] however, to the best of our knowledge, no total synthesis has been reported so far. In 2003, we embarked on a project directed toward the total synthesis of optically active GKK1032s and their analogues with the aim of exploring the structure−activity relationships. We have already reported our preliminary results concerning the enantioselective synthesis of the tricyclic decahydrofluorene model core **6**, which lacks two methyl groups at C9 and C11 (GKK1032s numbering) in the C-ring, by employing an intramolecular Diels−Alder (IMDA) cycloaddition strategy.[7] This work represents the first entry to the tricyclic core (ABC-ring) of the GKK1032s. Additionally, we have also disclosed an efficient and facile method for the construction of the characteristic alkyl aryl ether portion of the GKK1032s via Mitsunobu inversion.[8] In this paper, we wish to disclose the full details of our enantioselective synthesis of the model compound **6** as well as the real decahydrofluorene core **7** that stands for a fully elaborated ABC-ring system of the GKK1032s (**1**−**3**).

SCHEME 1. General Synthetic Strategy for GKK1032A$_2$ (2) by Employing Intramolecular Diels−Alder (IMDA) Reaction



Results and Discussion

Our general strategy for the synthesis of the GKK1032s is outlined in Scheme 1. The key element in this scheme consists of the intramolecular Diels−Alder (IMDA) reaction[9,10] of

(5) Oikawa, H. *J. Org. Chem.* **2003**, *68*, 3552.

(6) (a) Arai, N.; Ui, H.; Omura, S.; Kuwajima, I. *Synlett* **2005**, 1691. (b) Hasegawa, D.; Sakuma, Y.; Takagi, Y.; Uchiro, T. *The 125th Annual Meeting of the Pharmaceutical Society of Japan*; Tokyo, Japan, 2005, Abstract 4, 71. (c) Nagase, K.; Shiwaku, M.; Noyama, T.; Arakawa, Y.; Miyazaki, Y.; Kurosaka, J.; Munakata, R.; Takao, K.; Tadano, K. *89th Symposium on Organic Synthesis, Japan*, Symposium Paper; Tokyo, Japan, 2006, 45.

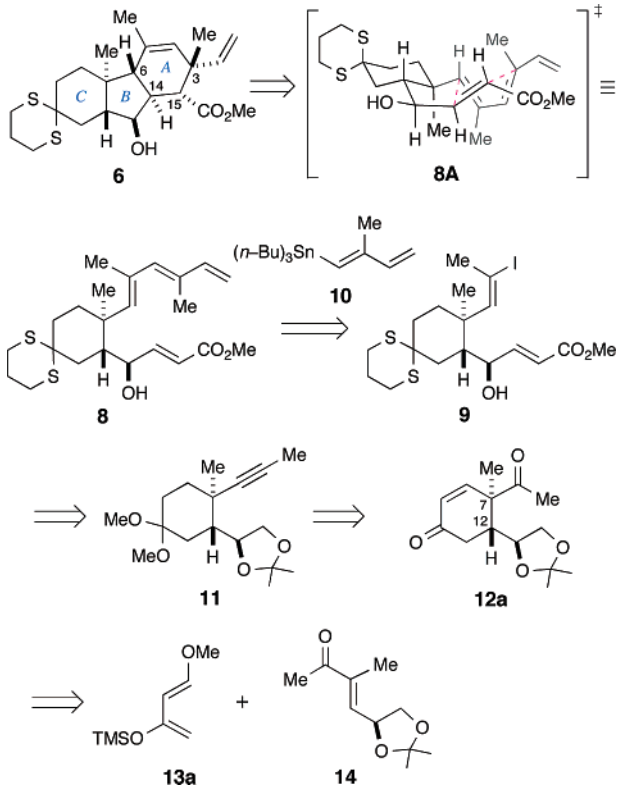
(7) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 1539.

(8) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 2599.

(9) For recent reviews on IMDA reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513. (b) Thomas, E. J. *Acc. Chem. Res.* **1991**, *24*, 229. (c) Fallis, A. G. *Pure Appl. Chem.* **1997**, *69*, 495. (d) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464. (e) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820. (f) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243. (g) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (h) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779.

(10) For selected recent reports on natural products syntheses based on the IMDA reactions, see the following. Lepicidin A: (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. Endiandlic acid A: (b) May, S. A.; Grieco, P. A.; Lee, H.-H. *Synlett* **1997**, 493. Ircinianin: (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691. Isopulo'upone: (d) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786. Lycopodine: (e) Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128. Bakkenolide: (f) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361. Equisetin: (g) Yuki, K.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2001**, *42*, 2517. Macquarimicins: (h) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029. (i) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4725. (j) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722. (k) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254. FR182877: (l) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (m) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. (n) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393. (o) Evans, D. A.; Starr, J. T. *J. Am. Chem.* Soc. **2003**, *125*, 13531. (p) Suzuki, T.; Tanaka, N.; Matsumura, T.; Hosoya, Y.; Nakada, M. *Tetrahedron Lett.* **2006**, *47*, 1593. Cochleamycin A: (q) Tatsuta, K.; Narazaki, F.; Kashiki, N.; Yamamoto, J.; Nakano, S. *J. Antibiot.* **2003**, *56*, 584. (r) Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441. Spinosyn A: (s) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955. Tubelactomicin A: (t) Motozaki, T.; Sawamura, A.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2261. (u) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2265. (v) Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439.

SCHEME 2. Retrosynthetic Analysis for Tricyclic Model Core 6 (ABC-Ring System) of GKK1032s

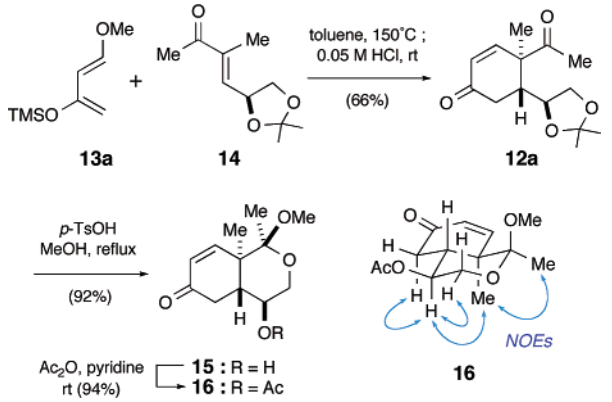


tetraene **II** to construct the tricyclic core **I** in one step; the structure **I** contains the requisite substituents, functional groups, and asymmetric carbon centers at C3, C6, C14, and C15. We envisaged that compound **I** would be elaborated to the targeted molecule **2** via a Mitsunobu-type alkyl aryl ether formation[8] and macrocyclization. To explore the feasibility of the designed IMDA reaction (**II** → **I**), we initially undertook model studies concerning construction of the tricyclic core **6** (cf. Figure 1) that lacks two methyl groups at C9 and C11 in the C-ring.

1. Synthesis of the Tricyclic Model Compound 6.

1.1. Synthetic Plan. We first pursued the synthesis of the tricyclic compound **6** as model studies. Our synthetic plan for the initial target **6** is outlined in Scheme 2. The crucial IMDA reaction of tetraene **8** would proceed via an *endo*-transition state such as **8A**, where both the A- and B-rings would be built up while controlling the stereochemistries at C3, C6, C14, and C15 (**8** → [**8A**] → **6**). The IMDA precursor **8** would be accessed in a straightforward manner by employing Stille coupling[11] of vinyl iodide **9** and vinylstannane **10**. Intermediate **9** would be derived from methyl ketone **12a** via methyl acetylene **11** by sequential functional group manipulation, protection, and deprotection or vice versa. Intermediate **12a** could, in turn, be accessed through an intermolecular Diels−Alder reaction[12] between the Danishefsky−Kitahara diene **13a**[13] and the known enulose derivative **14**,[14] where we believed that the requisite stereochemistry at C7 and C12 in **12a** should be created.

SCHEME 3. Synthesis of Intermediate 12a and Its Derivative 16



1.2. Synthesis of the Key Intermediate 12a. For the preparation of the key intermediate **12a**, we investigated the intermolecular Diels−Alder reaction between siloxydiene **13a**[13] and the known optically active enone **14**,[14] readily prepared from D-mannitol, as shown in Scheme 3. After several experiments, we found that the Diels−Alder reaction proceeded effectively by heating a mixture of **13a** and **14** in toluene in a sealed tube at 150 °C for 3 days; the desired cycloaddition product **12a** was obtained in 66% yield as the single diastereomer after hydrochloric acid treatment. The stereostructure of **12a** was proven by NOE studies of the transformed bicyclic enone **16**, which was prepared via a two-step sequence of reactions involving acid-catalyzed transacetalization of **12a** and acetylation of the resulting alcohol **15** (86% overall yield). The remarkable diastereoselectivity observed in this Diels−Alder reaction can be explained, as shown in Figure 2, by the preferential approach of diene **13a** to dienophile **14A** (**14**) from the opposite side of the bulky acetonide group, as previously reported by Ortuño and co-workers,[15] providing **12a** as the sole stereoisomer.

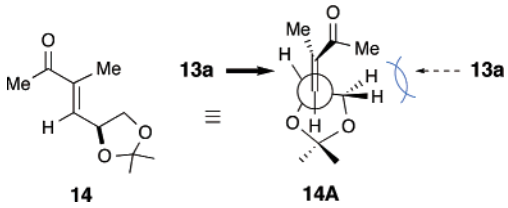


FIGURE 2. Consideration for the stereoselectivity on the Diels−Alder reaction between **14** (**14A**) and **13a**.

As shown in Scheme 4, compound **12a** was further converted to dimethylacetal **18** in 67% overall yield by hydrogenation of the olefinic double bond and subsequent regioselective acetal formation of the resulting cyclohexanone **17**. Vinyl triflate formation[16] [$KN(SiMe_3)_2$ (1.1 equiv), $PhNTf_2$ (1.6 equiv), THF, −78 °C] of **18** delivered the corresponding vinyl triflate **19**, which was immediately subjected to base-induced elimination/methylation[17] [LDA (3.0 equiv), MeI (5.0 equiv), THF, 0 °C]

(11) For recent reviews on Stille coupling reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (b) Kosugi, M.; Fugami, K. In *Handbook of Organopalladium Chemistry of Organic* Synthesis; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 263. (c) Espinet, P.; Echavarren, A. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(12) For reviews on the Diels−Alder reactions using siloxydienes, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. (c) Brownbridge, P. *Synthesis* **1983**, 85.

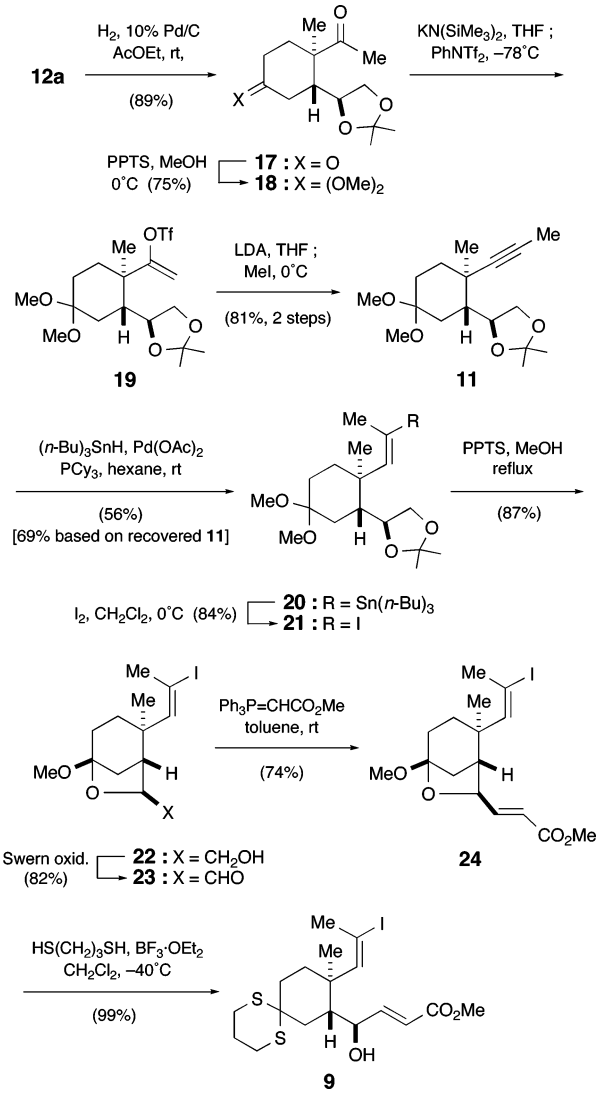
(13) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(14) (a) Izquierdo Cubero, I.; Portal Olea, M. D.; Garcia Poza, D. *Carbohydr. Res.* **1985**, *138*, 135. (b) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.

(15) Ortuño, R. M.; Ibarzo, J.; d'Angelo, J.; Dumas, F.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **1996**, *7*, 127.

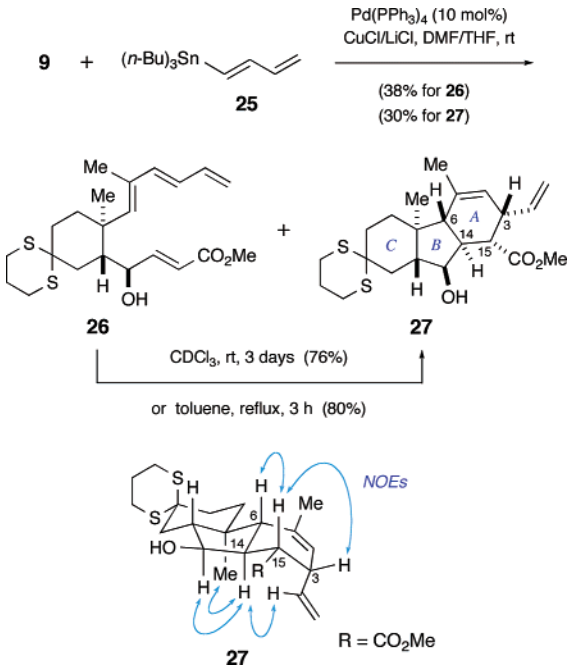
(16) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *14*, 4607.

SCHEME 4. Synthesis of Intermediate 9



to give methyl acetylene **11** in 81% overall yield from **18**. Transformation of **11** to vinyl iodide **21** was next examined under standard conditions such as radical-mediated hydrostannylation/iodination[18,19] [(*n*-Bu)$_3$SnH, AIBN; I$_2$], Pd(0)-catalyzed hydrostannylation/iodination[20] [(*n*-Bu)$_3$SnH, Pd(PPh$_3$)$_4$; I$_2$], or hydrozirconation/iodination[21] (Cp$_2$ZrHCl; I$_2$); however, unfortunately, poor yield of the expected product **21** was obtained in all cases. After several experiments, we were pleased to find that the use of Semmelhack's conditions[22] turned out to be the most reliable. Thus, treatment of **11** in hexane with a mixture of (*n*-Bu)$_3$SnH (10.0 equiv), Pd(OAc)$_2$ (0.3 equiv), and PCy$_3$ (0.6 equiv) at room temperature for 12 h provided the desired (*E*)-vinyl stannane **20** in 56% yield (69% yield based on recovery of **11**) with complete regioselectivity, which was then allowed to react with I$_2$ (1.5 equiv) to furnish the requisite vinyl iodide **21** in 84% yield.

SCHEME 5. Synthesis of Tricyclic Model Core 27 through an IMDA Reaction of Tetraene 26



In the next stage, we carried out installation of an α,*β*-unsaturated ester moiety that would serve as a dienophile in the devised key IMDA reaction. Acid-catalyzed hydrolysis of the acetonide moiety of **21** led to the formation of five-membered acetal **22** in 87% yield. Swern oxidation[23] of **22** (82% yield) followed by Wittig reaction of the resultant aldehyde **23** provided the desired (*E*)-α,*β*-unsaturated ester **24** (74% yield) along with its (*Z*)-isomer (14% yield), which were separated by silica gel column chromatography. Finally, exposure of **24** to 1,3-propanedithiol (5.0 equiv) in the presence of BF$_3$·Et$_2$O (2.4 equiv)[24] afforded the requisite key intermediate **9** in 99% yield.

1.3. Preliminary Investigations into the Construction of the Tricyclic Model Core 27 through an IMDA Reaction of Tetraene 26. Having obtained the key intermediate **9**, as shown in Scheme 5, we next pursued the model experiments for the construction of the tricyclic core **27** that lacks a methyl substituent at C3 in the A-ring; the sequence involved Stille coupling[11] of vinyl iodide **9** with the known vinylstannane **25**[25] and subsequent key IMDA reaction of the formed tetraene **26**. Corey and co-workers recently reported that Stille coupling was dramatically accelerated by the addition of CuCl;[26] therefore, we looked at the Corey protocol. Thus, treatment of **9** with **25** under Corey's improved conditions[26] [Pd(PPh$_3$)$_4$ (0.1 equiv), CuCl (1.0 equiv)/LiCl (1.0 equiv), DMF/THF, rt, 12 h] afforded the expected tetraene **26** in 38% yield. In this reaction, to our

(17) For examples of the conversion of methyl ketones to methyl acetylenes, see: (a) Schwede, W.; Cleve, A.; Ottow, E.; Wiechert, R. *Tetrahedron Lett*. **1993**, *34*, 5257. (b) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem*. **1980**, *45*, 2526 and references therein.

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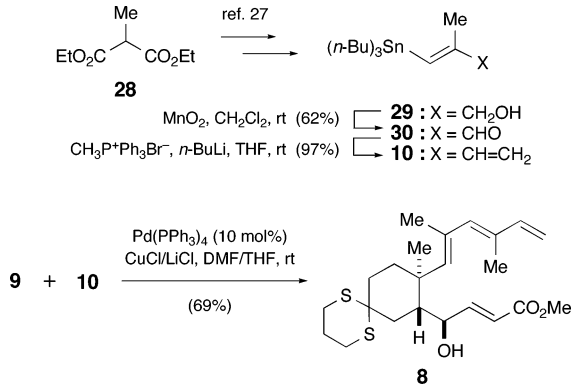
(22) Semmelhack, M. F.; Hooley, R. J. *Tetrahedron Lett*. **2003**, *44*, 5737.

(23) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Tidwell, T. T. *Synthesis* **1990**, 857. (c) Tidwell, T. T. *Org. React*. **1991**, *39*, 297.

(24) Zhou, W.-S. *Pure Appl. Chem*. **1986**, *58*, 817.

(25) Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Synthesis* **1993**, 943.

SCHEME 6. Synthesis of Tetraene 8, a Key IMDA Precursor



great surprise, the desired IMDA cycloaddition product **27** was also produced in 30% yield as the single stereoisomer. The stereostructure of **27** was proven by NOE measurements in the 500 MHz ^{1}H NMR spectrum; the newly formed stereochemistry at C3, C6, C14, and C15 was fully consistent with that of the GKK1032s. We also observed that leaving a solution of **26** in $CDCl_3$ at ambient temperature for 3 days resulted in the formation of **27** in 76% yield. In addition, expeditious conversion of **26** to **27** was efficiently achieved by refluxing a solution of **26** in toluene for 3 h.

1.4. Synthesis of the Tricyclic Core 6 Through an IMDA Reaction of Tetraene 8. Encouraged by the successful results described above, we next directed our attention to the synthesis of the tricyclic core **6**, which possesses a methyl substituent at C3 in the A-ring, by Stille coupling[11] of vinyl iodide **9** and vinylstannane **10** followed by IMDA reaction of the resulting tetaene **8** (Schemes 6 and 7). The requisite vinylstannane **10** was prepared in two steps from the known allyl alcohol **29**,[27] readily accessible from the commercially available diethyl methylmalonate **28**. Thus, oxidation of **29** with MnO_2 followed by Wittig olefination of the resulting aldehyde **30** with $Ph_3P{=}CH_2$ provided vinylstannane **10** in 60% yield for the two steps. Stille coupling of **9** with **10** under the same conditions used for the preliminary experiments (cf. **9** + **25** → **26** + **27**, Scheme 5) furnished the desired tetraene **8** in 69% yield. Contrary to the preliminary studies, no cycloaddition products were produced in this Stille coupling reaction. The difference in reactivity between tetraenes **8** and **26** must be attributed to the structural nature inherent in these molecules. Thus, as shown in Figure 3, in the case of **8**, *s-trans*-conformation **8B** might be preferentially formed rather than *s-cis*-conformation **8A** due to a steric interaction between C3-Me and C6-H (cf. **8A** vs **8B**); this phenomenon is obviously unfavorable for the IMDA reaction. On the other hand, in the case of **26**, there is no such steric interaction, facilitating the formation of the *s-cis*-conformation to produce the cycloadduct **27** even at ambient temperature.

As shown in Scheme 7, conversion of **8** to the targeted tricyclic core **6** through the key IMDA reaction was successfully achieved by heating a solution of **8** in toluene in a sealed tube with a small amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.5 equiv) at 120 °C for 24 h, giving rise to 61% yield of **6** as the isolated diastereomer. The stereostructure of **6** was confirmed by NOE experiments, proving that the stereochemistry at C3,

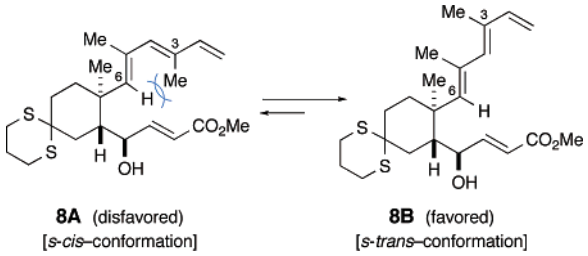
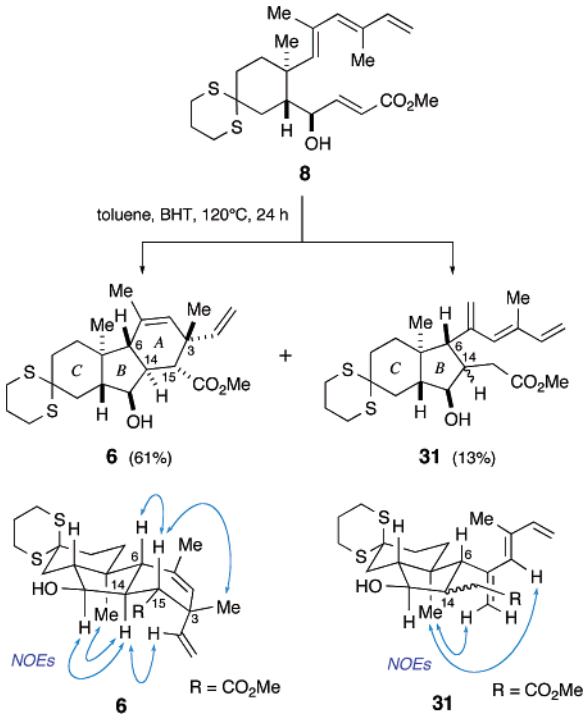


FIGURE 3. *s-cis*- and *s-trans*-Conformations **8A** and **8B**.

SCHEME 7. Synthesis of Tricyclic Core 6 through an IMDA Reaction of Tetraene 8



C6, C14, and C15 was fully identical with that of the GKK1032s. Interestingly, in this IMDA reaction a small amount (13% yield) of the indene derivative **31** was also generated as an inseparable mixture of the C14 epimers (ca. 2:1 by 500 MHz ^{1}H NMR); this byproduct **31** would be formed by an ene reaction[28,29] via transition states **8C** and **8D** as shown in Scheme 8.

2. Synthesis of the Fully Elaborated Tricyclic Core 7.

2.1. Synthetic Plan. Having established the synthetic pathway to the tricyclic model core **6**, we next conducted the synthesis of the fully elaborated tricyclic core **7** that represents the ABC-ring system of the GKK1032s (**1**−**3**).

Our synthetic plan for the final targeted compound **7** is outlined in Scheme 9, which is based on the model studies mentioned above. The targeted molecule **7** would be stereoselectively constructed by an IMDA reaction of the tetraene **32** via an *endo*-transition state **32A** (**32** → [**32A**] → **7**). The IMDA precursor **32** should be prepared from methyl acetylene **34** via Stille coupling of vinyl iodide **33** and vinylstannane **10** in a manner similar to that described in the model studies. Interme-

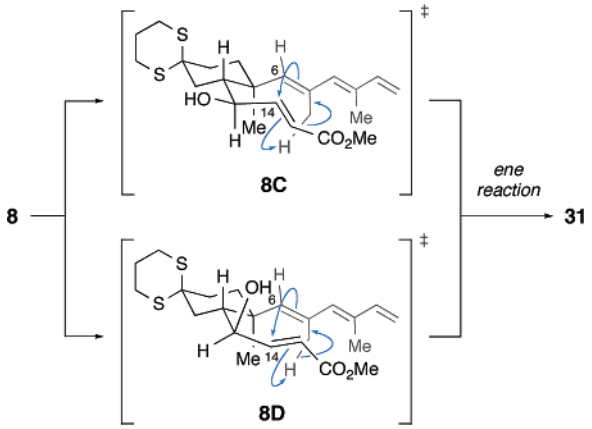
(26) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600.

(27) (a) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem*. **1996**, *61*, 6139. (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.

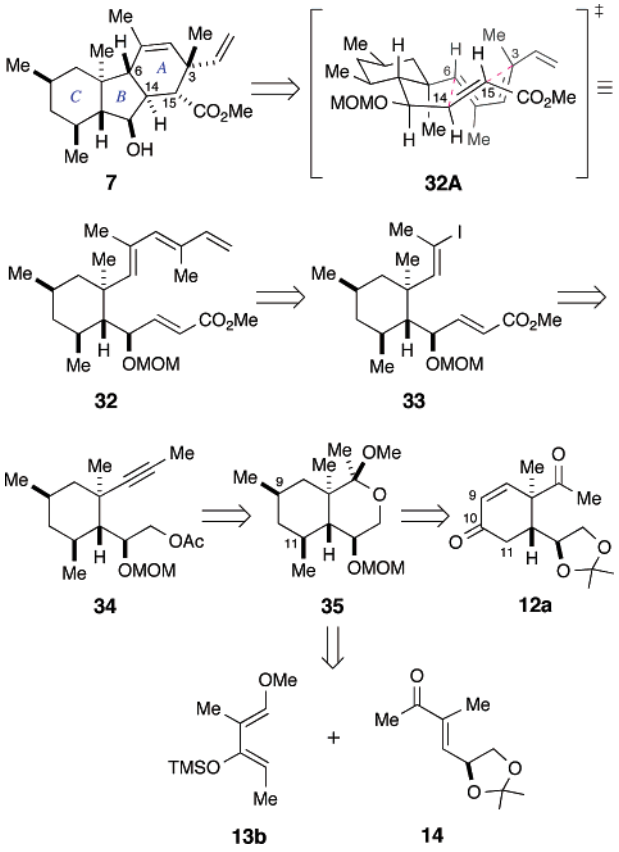
(28) For a review on intermolecular ene reaction, see: Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 1.

(29) An example of the ene reaction during Diels−Alder reaction, see: Campi, E. M.; Jackson, W. R. *Aust. J. Chem*. **1998**, *42*, 471.

SCHEME 8. Plausible Pathway to Indene Derivative 31 from Tetraene 8 through an Ene Reaction



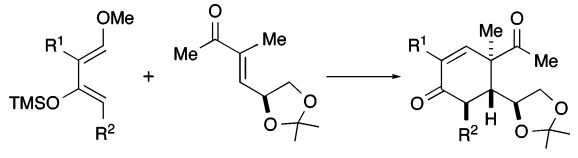
SCHEME 9. Retrosynthetic Analysis for Fully Elaborated Tricyclic Core 7 (ABC-Ring System of GKK1032S)



diate **34** could be derived from acetal **35** by appropriate elaboration. We envisioned that the access to **35** could be achieved by the stereocontrolled introduction of two methyl groups to the C9 and C11 positions in cyclohexenone **12a**, which was already prepared in section 1.2 (cf. Scheme 3). Alternatively, the intermediate **35** would be accessible more directly through an intermolecular Diels−Alder reaction[12] between dimethyl substituted siloxydiene **13b** and enone **14**.

2.2. Synthesis of the Key Intermediate 35. For a straightforward access to the key intermediate **35** possessing the two methyl groups at C9 and C11 in the C-ring, we initially investigated the intermolecular Diels−Alder reaction between (di)methylsiloxydienes **13b**−**d**[30] and enone **14**[14] as shown in Table 1. As mentioned in section 1.2 above, the reaction of

TABLE 1. Examinations of Intermolecular Diels−Alder Reaction between Siloxydienes 13a−d and Enone 14



entry	diene	R^1	R^2	conditions[b]	product	yield (%)[c]
1[a]	**13a**	H	H	toluene, 150 °C, 72 h	**12a**	66
2	**13b**	Me	Me	xylene, 190 °C, 72 h	**12b**	NR[d]
3	**13c**	Me	H	xylene, 190 °C, 72 h	**12c**	NR[d]
4	**13d**	H	Me	xylene, 190 °C, 72 h	**12d**	NR[d]

[a] This reaction was already carried out in section 1.2 (cf. Scheme 3). [b] All reactions were performed in a sealed tube. [c] Isolated yield. [d] NR: no reaction.

13a with **14** proceeded smoothly to form **12a** (entry 1); however, to our chagrin, all attempts to realize the Diels−Alder reactions between **13b**−**d** with **14** turned out to be fruitless; none of the desired cycloaddition products **12b**−**d** was obtained, and the starting materials **13b**−**d** and **14** were recovered unchanged even under harsh conditions (entries 2−4). We assumed that these failures were due to the very low reactivity of dienes **13b**−**d**, which may be attributed to the steric hindrance of the methyl group(s) present in siloxydienes **13b**−**d**. Consequently, we decided to elaborate the key intermediate **35** in a step-by-step manner starting from cyclohexenone **12a**; the sequence involved the regio- and stereoselective methylation at the C9 and C11 positions followed by elimination of the C10 carbonyl function.

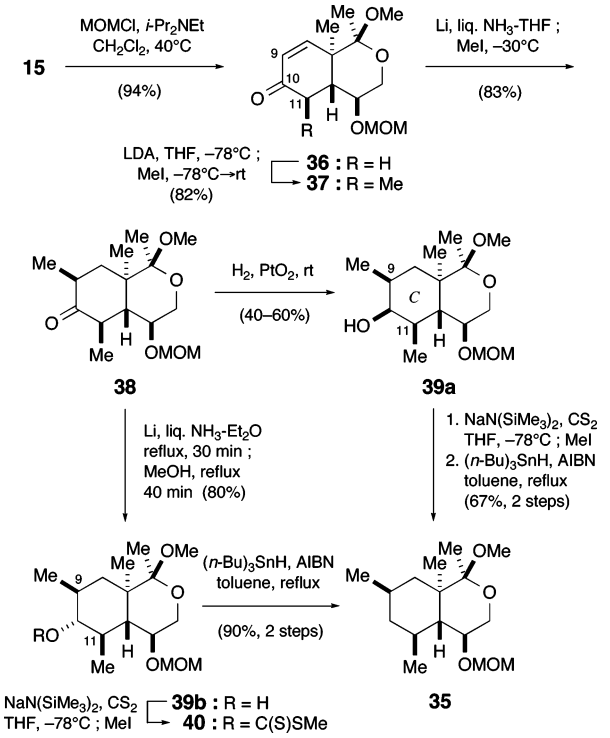
As shown in Scheme 10, compound **15** was converted to the MOM ether **36** in 94% yield by MOM protection of the secondary hydroxy group. The first methyl group was efficiently introduced to the C11 position by exposure of **36** to LDA (1.3 equiv) at −78 °C followed by addition of MeI (2.0 equiv), giving rise to enone **37** in 82% yield with complete stereoselectivity. Subsequent Birch reduction of **37** generated the corresponding lithium enolate, which was then methylated in situ with MeI (3.0 equiv) to deliver dimethylcyclohexanone **38** in 83% yield as the sole stereoisomer. The stereostructure of **38** was proven by X-ray crystallographic analysis[31] of the transformed cyclohexanol **39a**, which was prepared by hydrogenation of **38** in the presence of a catalytic amount of PtO_2 (40−60% yield). The secondary hydoroxy group in **39a** was then eliminated by using the Barton−McCombie protocol.[32] Thus, treatment of **39a** with $NaN(SiMe_3)_2$ (2.0 equiv) in THF at −78 °C followed by addition of CS_2 (3.0 equiv) and MeI (5.0 equiv) at the same temperature, furnished the corresponding methyl xanthate. This was allowed to react with $(n\text{-Bu})_3SnH$ (2.3 equiv) in toluene in the presence of a catalytic amount of AIBN (0.1 equiv) at 110 °C, providing the desired deoxygenated product **35** in 67% overall yield from **39a**. Although we were able to develop a pathway to **35** from **38**, we encountered

(30) For a synthesis of **13b**, see: (a) Myles, D. C.; Bigham, M. H. *Org. Synth.* **1992**, *70*, 231. For a synthesis of **13c**, see: (b) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976. For a synthesis of **13d**, see: (c) Burger, M. T.; Still, W. C. *J. Org. Chem.* **1996**, *61*, 775.

(31) X-ray ORTEP drawing of **39a** and detailed crystallographic data are provided in Supporting Information.

(32) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Izuhara, T.; Katoh, T. *Org. Lett.* **2001**, *3*, 1653. (c) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 4207. (d) Katoh, T.; Izuhara, T.; Yokota, W.; Inoue, M.; Watanabe, K.; Nobeyama, A.; Suzuki, T. *Tetrahedron* **2006**, *62*, 1590.

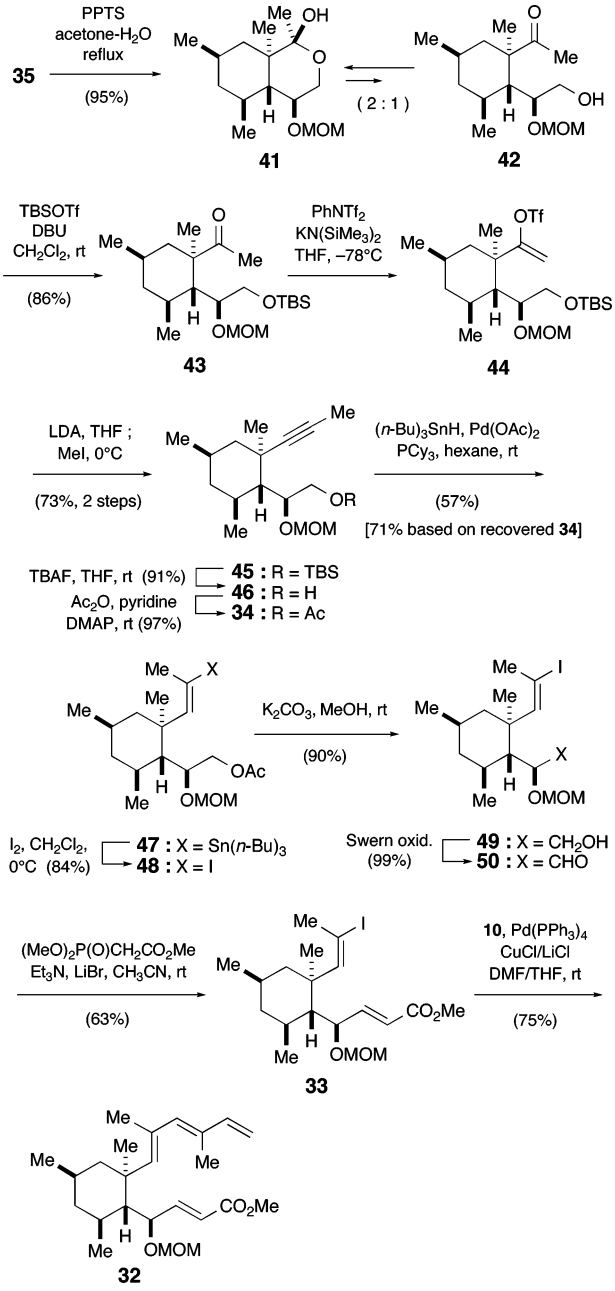
SCHEME 10. Synthesis of Intermediate 35



problems with a large-scale operation in the hydrogenation step (**38** → **39a**); the yields of **39a** were reduced to ~40%. Several attempts to realize reduction of **38** using other reducing agents such as $NaBH_4$, $LiAlH_4$, and DIBALH resulted in failure; considerable epimerization at C9 and/or C11 was observed in the reduction product **39a**. Eventually, to our delight, we found that Birch reduction was quite effective for this purpose; the reduction product **39b** was obtained in 80% yield without any epimerization at C9 and/or C11. Compound **39b** was efficiently converted to the desired cyclohexane derivative **35** in 90% overall yield via methyl xanthate **40** similarly employing the Barton−McCombie protocol.[32]

2.3. Synthesis of the Key IMDA Precursor 32. With the requisite dimethylcyclohexane **35** in hand, we next focused our attention on elaboration of the key IMDA precursor **32** as shown in Scheme 11. Acidic hydrolysis of methylacetal **35** followed by silylation of an equilibrium mixture of the resulting δ-lactol **41** and methyl ketone **42** (2:1 in $CDCl_3$ by 500 MHz ^1H NMR) afforded TBDMS ether **43** in 82% yield for the two steps. Compound **43** was further converted to methyl acetylene **45** in 73% overall yield through a two-step sequence involving vinyl triflate formation[16] [$KN(SiMe_3)_2$ (2.1 equiv), $PhNTf_2$ (2.6 equiv), THF, −78 °C] and base-induced elimination/methylation[17] [LDA (3.6 equiv), THF, −78 °C; MeI (3.3 equiv), −78 → 0 °C] of the formed vinyl triflate **44**. Hydrostannylation of **45** was next examined by employing Semmelhack's conditions[22] identical to those used on **11** (cf. **11** → **21**, Scheme 4); however, in this case the expected vinyl stannane was not obtained, and the starting material **45** was recovered unchanged. We reasoned that this failure arose from the presence of a bulky TBDMS protecting group within **45** that would interrupt the reaction. After several trials, the desired hydrostannylation was successfully realized by exchanging the TBDMS group with a less bulky acetyl group. Thus, deprotection of the TBDMS group in **45** with tetra-*n*-butylammonium fluoride (TBAF) and subsequent acetylation of the liberated alcohol **46** provided the corresponding acetate **34** in 88% overall yield. Hydrostannylation of **34** under Semmelhack's conditions,[22] as we expected, proceeded satisfactorily to afford the requisite vinyl stannane **47** in 57% yield (71% yield based on recovery of **34**). Subsequent treatment of **47** with I_2 (2.0 equiv) furnished the desired vinyl iodide **48** in 84% yield.

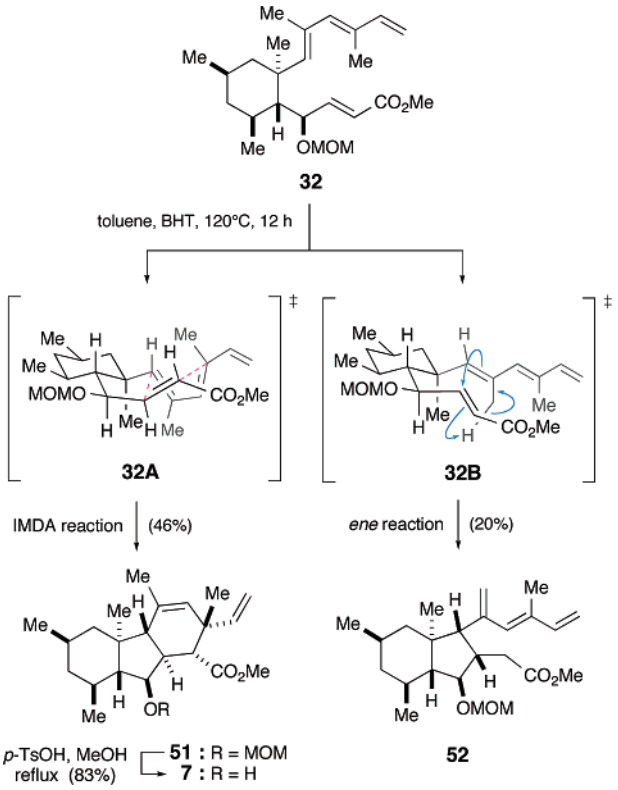
SCHEME 11. Synthesis of Key IMDA Precursor 32



In the next stage, we further investigated the installation of the dienophile and diene moieties required for the key IMDA reaction. Toward this end, alkali hydrolysis of the acetyl group in **48** followed by Swern oxidation[23] delivered aldehyde **50** in 89% overall yield. Initial attempts to realize Wittig reaction of **50** with $Ph_3P{=}CH_2CO_2Me$ met with failure; however, Horner−Emmons reaction[33] using $(MeO)_2P(O)CH_2CO_2Me$ provided the desired α,β-unsaturated ester **33** in 63% yield. Finally, Stille coupling of **33** with vinyl stannane **10** was carried out under

(33) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

SCHEME 12. Synthesis of Fully Elaborated Tricyclic Core 7 via IMDA Reaction of Tetraene 32



Corey's improved conditions,[26] which furnished the requisite tetraene **32**, a key IMDA precursor, in 75% yield.

2.4. Synthesis of the Decahydrofluorene 7, a Fully Elaborated Tricyclic Core of the GKK1032s, through an IMDA Reaction of Tetraene 32. Having obtained the key IMDA precursor **32** in an efficient way, the stage was now set for the crucial IMDA reaction of **32** to access the final targeted molecule **7**, a fully elaborated tricyclic core (ABC-ring) of the GKK1032s. As shown in Scheme 12, the key IMDA reaction of **32** was carried out under the same conditions (toluene, BHT, 120 °C, 24 h) employed in section 1.4. The desired decahydrofluorene **51** was obtained in 46% yield as the sole IMDA product along with a 20% yield of the undesired indene derivative **52** that was presumably generated through an ene reaction via a transition state such as **32B**. The stereostructures of both **51** and **52** were confirmed by NOESY experiments, respectively, as depicted in Figure 4; the stereochemistry within **51** was again fully identical with that of GKK1032s (**1**−**3**). Deprotection of the MOM group in **51** under conventional conditions furnished the final target **7** in 83% yield.

We further investigated Lewis acid mediated IMDA reaction of tetraene **32**, as shown in Table 2, in the hope that the formation of the undesired ene reaction product **52** would be

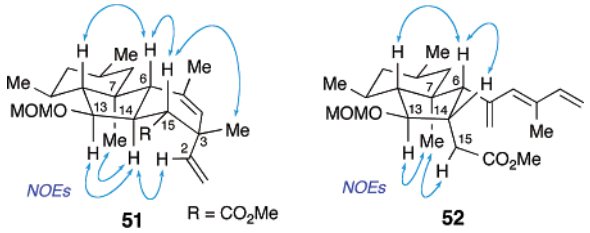
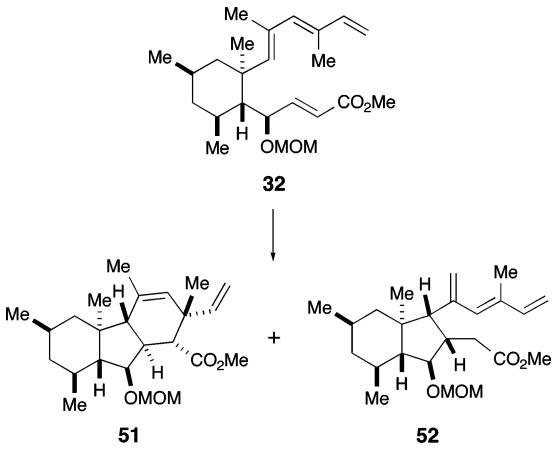


FIGURE 4. Selected NOESY Correlation of Compounds **51** and **52**.

TABLE 2. Screening of Lewis Acids for IMDA Reaction of Tetraene 32



		yield (%)[a]	
entry	conditions	**51**	**52**
1	Et_2AlCl (0.87 M in hexane), toluene, −40 °C, 2 h	76	trace[b]
2	$LiClO_4$ (1.8 M in Et_2O), Et_2O, 0 °C → rt	decomp	
3	$ZnCl_2$ (1.0 M in Et_2O), CH_2Cl_2, 0 °C → rt	decomp	

[a] Isolated yield. [b] A trace amount (<2%) of **52** could be detected in the 500 MHz ^1H NMR spectrum of the crude reaction mixture.

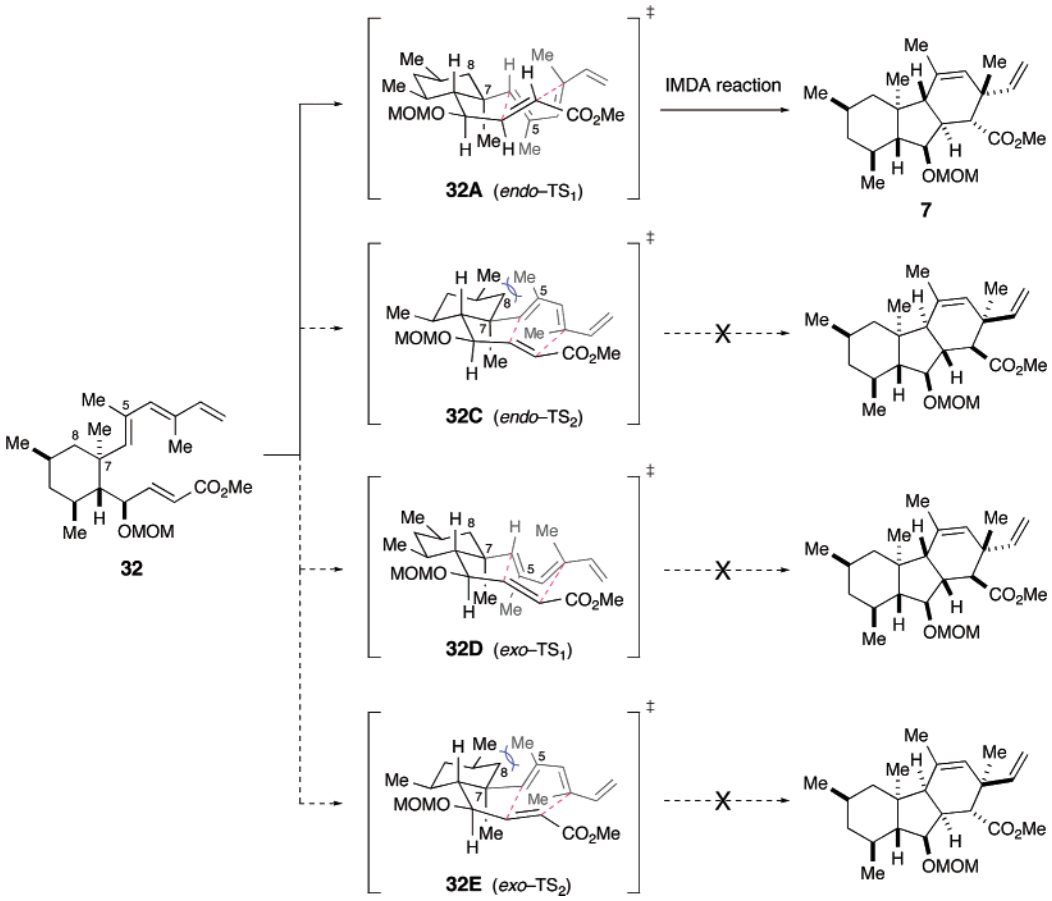
suppressed at rather low temperatures. After several experiments, we were pleased to find that the desired IMDA reaction proceeded efficiently by the use of Et_2AlCl (entry 1). Thus, treatment of **32** with Et_2AlCl (2.0 equiv) in toluene at −40 °C for 2 h provided 76% yield of the desired IMDA product **51** along with a trace amount (<2% yield) of the ene reaction product **52**. When $LiClO_4$ or $ZnCl_2$ was used as a Lewis acid, the requisite **51** was not formed and only unidentified decomposition products were generated in the reaction mixture (entries 2 and 3).

The remarkable stereochemical outcome observed in the IMDA reactions (cf. **8** → **6**, Scheme 7; **32** → **51**, Scheme 12 and Table 2) can be rationalized as follows. With respect to the *endo*/*exo*- and π-facial selectivity, as depicted in Scheme 13, four possible transition states such as **32A** (*endo*-TS_1), **32C** (*endo*-TS_2), **32D** (*exo*-TS_1), and **32E** (*exo*-TS_2), are considered. Among them, the two *endo*-TSs (**32A** and **32C**) are more favorable than the two *exo*-TSs (**32D** and **32E**) as a result of the so-called secondary orbital interaction between the diene and dienophile moieties. Comparing the two *endo*-TSs (**32A** and **32C**), the former is favored because the latter suffers a severe steric repulsion ($A^{1,3}$ strain) between the C5 methyl group and C7−C8 carbon bond in the cyclohexane ring. As a result, the IMDA reaction must have proceeded exclusively through an *endo*-TS_1 such as **32A**, leading to the predominant formation of the desired decahydrofluorene **51** with complete stereoselectivity.

Conclusion

We have accomplished the enantioselective synthesis of the fully elaborated tricyclic decahydrofluorene core **7** (ABC-ring system) of GKK1032s, novel antibiotic antitumor agents, for the first time. A strategic IMDA reaction of tetraene **32** was employed to effectively build up the desired ABC-ring system while controlling the stereogenic centers at C3, C6, C14, and C15 (**32** → **51**, Scheme 12 and Table 2). Access to the substrate

SCHEME 13. Four Possible *endo*- and *exo*-Transition States (TSs) in the IMDA Reaction of Tetraene 32



for the IMDA reaction involved the following crucial steps: (i) the intermolecular Diels−Alder reaction of siloxydiene **13a** and enantiomerically pure enone **14** to form the appropriately functionalized C-ring portion **12a** (cf. **13a** + **14** → **12a**, Scheme 3), (ii) the efficient conversion of methyl ketone **43** to vinyl iodide **48** via sequential vinyl triflate formation, base-induced elimination/methylation, and Pd-catalyzed hydrostannylation/iodination (cf. Scheme 11), and (iii) CuCl-promoted Stille coupling of vinyl iodide **33** and vinylstannane **10** to install the requisite triene side chain (**33** + **10** → **32**, Scheme 11). On the basis of the present research, total synthesis of GKK1032s and related natural products is currently under investigation in our laboratories.

Experimental Section

Procedure for Stille Coupling of Vinyl Iodide 9 with Vinylstannane 25 and Subsequent IMDA Reaction: (1′*R*,2′*R*)-2′-[(1*R*,2*E*)-1-Hydroxy-3-methoxycarbonyl-2-propenyl]-1′-[(1*E*,3*E*)-2-methylhexa-1,3,5-trienyl]-1′-methyl-spiro[1,3-dithiane-2,4′-cyclohexane] (26) and (1′*S*,2′*S*,4a′*S*,4b′*S*,8a′*R*,9′*R*,9a′*S*)-4′,4b′-Dimethyl-9′-hydroxy-1′-methoxycarbonyl-2′-vinyl-spiro[1,3-dithinane-2,7′-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1*H*-fluorene] (27). Tetrakis(triphenylphosphine)palladium(0) (20.0 mg, 17 μmol), copper(I) chloride (17.0 mg, 0.17 mmol), and lithium chloride (7.4 mg, 0.17 mmol) were added successively to a stirred solution of vinyl iodide **9** (41.0 mg, 85 μmol) and vinylstannane **25** (58.5 mg, 0.17 mmol) in a mixture of dry DMF (3.0 mL) and dry THF (3.0 mL) at room temperature. After 13 h, the reaction mixture was diluted with ethyl acetate (60 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane−ethyl acetate, 30:1 → 4:1) to give **26** (13.2 mg, 38%) and **27** (10.4 mg, 30%).

Compound **26**: pale yellow oil; $[\alpha]^{20}_D$ +29.7 (*c* 0.44, $CHCl_3$); IR (neat) 650, 731, 779, 874, 906, 984, 1001, 1097, 1165, 1194, 1240, 1275, 1435, 1624, 1655, 1705, 1720, 2910, 2933, 3465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23−1.44 (m, 2H), 1.30 (s, 3H), 1.45−1.50 (m, 1H), 1.96 (s, 3H), 1.70−2.27 (m, 6H), 2.31 (dt, *J* = 12.4, 2.7 Hz, 1H), 2.64−2.74 (m, 2H), 2.82−2.90 (m, 2H), 3.73 (br s, 3H), 4.46−4.55 (m, 1H), 5.03−5.09 (m, 1H), 5.21 (dd, *J* = 1.5, 16.8 Hz, 1H), 5.46 (br s, 1H), 6.00 (dd, *J* = 1.9, 15.6 Hz, 1H), 6.15−6.21 (m, 2H), 6.30−6.43 (m, 1H), 6.90 (dd, *J* = 4.3, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.0, 21.3, 25.9, 26.0, 26.3, 32.4, 33.6, 34.5, 39.7, 44.8, 50.1, 51.6, 71.4, 116.4, 119.7, 127.1, 134.5, 140.0, 143.4, 151.1, 166.7; HREIMS (*m*/*z*) calcd for $C_{22}H_{32}O_3S_2$ (M^+), 408.1793, found 408.1793.

Compound **27**: colorless prisms (recrystallization from hexane−Et_2O); mp 56−58 °C; $[\alpha]^{20}_D$ +90.8 (*c* 0.15, $CHCl_3$); IR (neat) 731, 783, 802, 903, 1043, 1159, 1211, 1238, 1333, 1373, 1435, 1734, 2933, 3483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.78 (s, 3H), 1.75 (s, 3H), 1.70−1.80 (m, 2H), 1.80−1.85 (m, 2H), 1.90−2.10 (m, 3H), 2.01−2.10 (m, 2H), 2.10−2.18 (m, 1H), 2.23 (dt, *J* = 8.1, 11.8 Hz, 1H), 2.56 (dt, *J* = 13.3, 2.3 Hz, 1H), 2.69 (ddd, *J* = 3.1, 6.9, 14.3 Hz, 1H), 2.78−2.89 (m, 2H), 2.94 (dd, *J* = 6.6, 11.8 Hz, 1H), 3.02 (ddd, *J* = 3.1, 9.8, 14.3 Hz, 1H), 3.20−3.29 (m, 1H), 3.67 (s, 3H), 4.08 (dt, *J* = 7.9, 3.6 Hz, 1H), 5.00−5.07 (m, 2H), 5.12 (t, *J* = 1.5 Hz, 1H), 5.67 (ddd, *J* = 8.3, 10.5, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 21.3, 25.9, 26.1, 26.4, 34.6, 35.1, 35.4, 40.8, 41.2, 43.9, 45.7, 50.4, 51.5, 54.7, 54.8, 72.5, 117.0, 125.0, 137.4, 137.8, 175.5; HREIMS (*m*/*z*) calcd for $C_{22}H_{32}O_3S_2$ (M^+), 408.1793, found 408.1787.

A solution of **26** (8.0 mg, 20 μmol) in $CDCl_3$ (0.5 mL) was allowed to stand at room temperature for 3 days to give **27** (6.1 mg, 76%) after purification by column chromatography (hexane−ethyl acetate, 10:1 → 4:1). The ^{1}H NMR spectrum of this sample was identical with that recorded for compound **27**.

A solution of **26** (10.2 mg, 25 μmol) in toluene (1.0 mL) was heated at reflux for 3 h to provide **27** (8.2 mg, 80%) after purification by column chromatography (hexane−ethyl acetate, 10:1 → 4:1). The ^{1}H NMR spectrum of this sample was identical with that recorded for **27**.

Procedure for IMDA Reaction of Tetraene 26: (1′*S*,2′*S*,4a′*S*,4b′*S*,8a′*R*,9′*R*,9a′*S*)-9′-Hydroxy-1′-methoxycarbonyl-2′,4′,4b′-trimethyl-2′-vinyl-spiro[1,3-dithiane-2,7′-2′,4a′,4b′,5′,6′,7′,8′,8a′,9′,9a′-decahydro-1*H*-fluorene] (6) and (1′*R*,2′*RS*,3′*S*,3a′*S*,7a′*R*)-1′-Hydroxy-2′-(2-methoxycarbonyl)methyl-3a′-methyl-3′-[(*E*)-4-methylhexa-1,3,5-trien-2-yl]-spiro[1,3-dithiane-2,6′-octahydro-1*H*-indene (31). A solution of tetraene **8** (14 mg, 23 μmol) in dry toluene (3.0 mL) in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.5 mg, 12 μmol) was heated at 120 °C in a sealed tube for 24 h. After cooling, the mixture was concentrated in vacuo to give a residue, which was purified by column chromatography (hexane−ethyl acetate, 20:1 → 5:1) to furnish **6** (8.5 mg, 61%) and **31** (1.8 mg, 13%).

Compound **6**: colorless needles (recrystallization from hexane−Et_2O); mp 163−166 °C; $[\alpha]^{20}_D$ +65.7 (*c* 0.85, $CHCl_3$); IR (neat) 607, 621, 688, 783, 804, 852, 908, 995, 1047, 1159, 1223, 1259, 1331, 1375, 1435, 1716, 2875, 2931, 3500 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (s, 3H), 1.28 (s, 3H), 1.42−1.53 (m, 1H), 1.69−1.83 (m, 3H), 1.75 (s, 3H), 1.89−2.00 (m, 3H), 2.00−2.10 (m, 2H), 2.11−2.18 (m, 1H), 2.33 (dt, *J* = 8.3, 12.0 Hz, 1H), 2.52 (dt, *J* = 13.4, 2.2 Hz, 1H), 2.61 (d, *J* = 12.0 Hz, 1H), 2.65−2.75 (m, 1H), 2.77−2.87 (m, 2H), 2.95−3.03 (m, 1H), 3.68 (s, 3H), 3.93−3.99 (m, 1H), 4.85 (s, 1H), 4.98 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.05 (dd, *J* = 1.5, 10.4 Hz, 1H), 5.69 (dd, *J* = 10.4, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 21.2, 25.9, 26.1, 26.4, 26.7, 34.5, 35.0, 35.3, 41.3, 42.4, 44.0, 50.3, 51.3, 52.3, 54.4, 55.5, 72.7, 114.5, 131.3, 135.4, 142.8, 174.8; HREIMS (*m*/*z*) calcd for $C_{23}H_{34}O_3S_2$ (M^+), 422.1949, found 422.1950.

Compound **31**: pale yellow oil; $[\alpha]^{20}_D$ +25.6 (*c* 0.18, $CHCl_3$); IR (neat) 667, 752, 901, 989, 1174, 1205, 1236, 1255, 1277, 1331, 1340, 1379, 1415, 1437, 1601, 1622, 1720, 2925, 2949, 3948 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 1/3H), 0.93 (s, 2/3 × 3H), 1.55−1.70 (m, 1H), 1.70−1.90 (m, 3H), 1.87 (s, 1/3H), 1.91 (s, 2/3H), 1.88−1.99 (m, 2H), 1.97−2.10 (m, 3H), 2.35−2.48 (m, 2H), 2.56−2.73 (m, 3H), 2.74−2.83 (m, 1H), 2.85−2.95 (m, 1H), 3.01−3.10 (m, 1H), 3.55 (d, *J* = 2.1 Hz, 1/3H), 3.58 (d, *J* = 2.0 Hz, 2/3H), 3.57−3.67 (m, 1H), 3.68 (s, 3H), 5.02 (s, 1/3H), 5.05 (s, 2/3H), 5.08 (d, *J* = 10.7 Hz, 2/3H), 5.12 (d, *J* = 10.9 Hz, 1/3H), 5.18 (s, 1/3H), 5.21 (s, 2/3H), 5.21 (d, *J* = 17.4 Hz, 2/3H), 5.28 (d, *J* = 17.4 Hz, 1/3H), 5.76 (br s, 1/3H), 5.80 (br s, 2/3H), 6.37 (dd, *J* = 10.7, 17.4 Hz, 2/3 × 1H), 6.92 (dd, *J* = 10.9, 17.4 Hz, 1/3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4 (2/3C), 13.6 (1/3C), 16.1 (2/3C), 16.2 (1/3C), 17.5 (1/3C), 20.3 (2/3C), 25.9 (2/3C), 26.0 (2/3C), 26.4 (2/3C), 26.9 (1/3C), 27.9 (1/3C), 29.7 (1/3C), 34.3, 34.7, 37.3 (2/3C), 37.4 (1/3C), 42.8, 45.4 (2/3C), 45.5 (1/3C), 50.1, 50.5 (1/3C), 50.6 (2/3C), 51.9, 57.3 (1/3C), 57.5 (2/3C), 80.0, 113.2 (2/3C), 114.8 (1/3C), 118.1 (2/3C), 119.1 (1/3C), 133.2 (1/3C), 134.7 (2/3C), 135.1 (1/3C), 135.4 (2/3C), 141.7, 142.4, 175.6; HREIMS (*m*/*z*) calcd for $C_{23}H_{34}O_3S_2$ (M^+), 422.1949, found 422.1951.

Procedure for IMDA Reaction of Tetraene 32: (1*R*,2*S*,4a*S*,4b*S*,6*R*,8*S*,8a*R*,9*R*,9a*S*)-9- Methoxymethoxy-2,4,4b,6,8-pentamethyl-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1*H*-fluorene-1-carboxylic acid methyl ester (51) and [(1*R*,2*S*,3*S*,3a*S*,5*R*,7*S*,7a*R*)-1-Methoxymethoxy-3a,5,7- trimethyl-3-[(*E*)-4-methylhexa-1,3,5-trien-2-yl]octahydro-1*H*-inden-2-yl]acetic acid methyl ester (52). (a) Under Thermal Conditions. A solution of **32** (7.0 mg, 18 μmol) in dry toluene (2.0 mL) in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.0 mg, 9.0 μmol) was heated at 120 °C in a sealed tube for 12 h. After cooling, the mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane−ethyl acetate, 40:1 → 8:1) to give **51** (3.2 mg, 46%) and **52** (1.4 mg, 20%).

Compound **51**: colorless oil; $[\alpha]^{20}_D$ +114.2 (*c* 0.32, $CHCl_3$); IR (neat) 667, 756, 862, 920, 999, 1036, 1045, 1068, 1099, 1157, 1211, 1230, 1255, 1325, 1375, 1435, 1454, 1732, 2925, 2949 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (q, *J* = 12.1 Hz, 1H), 0.75 (s, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 12.1 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.14 (t, *J* = 6.0 Hz, 1H), 1.26 (s, 3H), 1.55−1.68 (m, 1H), 1.68−1.80 (m, 1H), 1.75−1.88 (m, 1H), 1.76 (s, 3H), 1.92 (dd, *J* = 4.1, 12.1 Hz, 1H), 1.98 (d, *J* = 12.0 Hz, 1H), 2.36 (dt, *J* = 7.2, 12.0 Hz, 1H), 2.62 (d, *J* = 12.0 Hz, 1H), 3.29 (s, 3H), 3.65 (s, 3H), 3.82 (dd, *J* = 6.0, 7.2 Hz, 1H), 4.44 (d, *J* = 5.9 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.88 (s, 1H), 4.95 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.02 (dd, *J* = 1.6, 10.4 Hz, 1H), 5.67 (dd, *J* = 10.4, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 20.6, 21.9, 22.8, 26.7, 28.1, 29.5, 42.9, 43.3, 43.4, 46.3, 48.5, 50.9, 51.9, 53.5, 56.0, 66.4, 80.0, 97.8, 114.0, 131.6, 135.3, 143.3, 174.0; HREIMS (*m*/*z*) calcd for $C_{24}H_{38}O_4$ (M^+), 390.2770, found 390.2770.

Compound **52**: colorless oil; $[\alpha]^{20}_D$ +43.2 (*c* 0.14, $CHCl_3$); IR (neat) 733, 877, 899, 1036, 1105, 1138, 1157, 1167, 1192, 1246, 1259, 1383, 1435, 1454, 1736, 2908, 2922, 2949 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50−0.64 (m, 1H), 0.68−0.78 (m, 1H), 0.85 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 3H), 0.94 (d, *J* = 6.2 Hz, 3H), 1.03 (t, *J* = 10.0 Hz, 1H), 1.60−1.78 (m, 4H), 1.87 (s, 3H), 2.55 (d, *J* = 9.6 Hz, 1H), 2.55−2.67 (m, 2H), 2.71−2.80 (m, 1H), 3.35 (s, 3H), 3.53 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.56 (s, 3H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 5.04 (d, *J* = 10.9 Hz, 1H), 5.04 (s, 1H), 5.17 (d, *J* = 17.3 Hz, 1H), 5.26 (s, 1H), 5.83 (s, 1H), 6.38 (dd, *J* = 10.9, 17.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 16.7, 20.5, 22.6, 27.6, 30.1, 37.8, 43.4, 44.4, 45.8, 47.7, 51.4, 56.1, 57.8, 60.9, 88.8, 96.6, 112.6, 117.9, 134.8, 135.2, 142.1, 142.8, 173.6; HREIMS (*m*/*z*) calcd for $C_{24}H_{38}O_4$ (M^+), 390.2770, found 390.2761.

(b) Under Lewis Acid Conditions. Diethylaluminum chloride in hexane (0.87 M solution, 52 mL, 46 μmol) was added slowly to a stirred solution of **32** (8.9 mg, 23 μmol) in dry toluene (2.5 mL) at −40 °C under argon. After 2 h, the reaction was quenched with 15% aqueous Rochelle salt (8 mL) at −40 °C, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with 3% aqueous HCl (2 × 6 mL), saturated aqueous $NaHCO_3$ (2 × 6 mL), and brine (2 × 6 mL), andthen dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane−ethyl acetate, 30:1 → 10:1) to give **51** (7.0 mg, 76%) as a colorless oil; $[\alpha]^{20}_D$ +114.8 (*c* 0.70, $CHCl_3$). The ^{1}H NMR spectrum of this sample were identical with those described in (a).

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all other new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. X-ray crystallographic information for **39a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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