

Gassman's Intramolecular [2 + 2] Cationic Cycloaddition. Formal Total Syntheses of Raikovenal and *epi*-Raikovenal

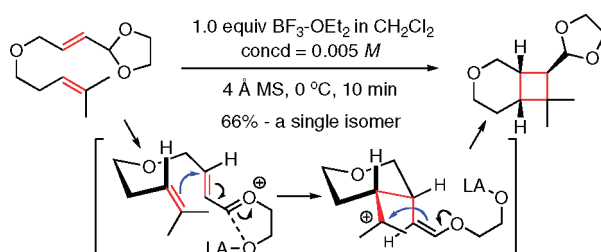
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ABSTRACT



The first intramolecular version of Gassman's cationic [2 + 2] cycloaddition employing vinyl acetals tethered to an unactivated olefin and its application in the formal syntheses of raikovenal and *epi*-raikovenal are described.

In the past half-century, a diverse array of elegant work from the synthetic community has established the [2 + 2] cycloaddition along with Diels–Alder-type cycloadditions as one of the most powerful cycloaddition manifolds in organic synthesis.¹ With the Woodward–Hoffmann rules as the fundamental guiding principles,² photochemical [2 + 2]

cycloadditions^{3–7} have naturally taken center stage and played a significant role in establishing the current prominence of this cycloaddition in synthesis. On the other hand, a nonphotochemical or thermal [2 + 2] cycloaddition strategy remains less developed.⁸ Some elegant advances have been made in this area with most being stepwise transformations whether mediated by metals or acids.^{9–11} However, what has been under-explored is Gassman's cationic [2 + 2] cycloadd-

(1) For general reviews on cycloadditions, see: (a) Chapters on cycloadditions in: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vols. 4 and 5. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford and New York, 1990. (c) Padwa, A.; Schoffstall, A. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2.

(2) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, 8, 781.

(3) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 123.

(4) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, 95, 2003.

(5) Bach, T. *Synthesis* **1998**, 683, and refs 1–15 cited within.

(6) (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, 103, 1449. (b) De Keukeleire, D.; He, S.-L. *Chem. Rev.* **1993**, 93, 359. (c) Lukina, M. Yu. *Russ. Chem. Rev.* **1963**, 32, 635.

(7) Wong, H. N. C.; Lau, K. L.; Tam, K. F. *Top. Curr. Chem.* **1986**, 133, 83.

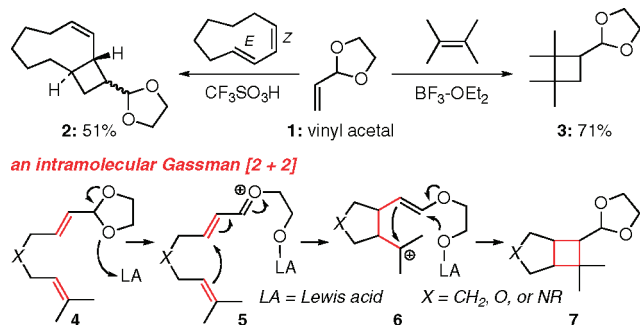
(8) For a review on thermal [2 + 2], see: (a) Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 63. (b) Narasaka, K.; Hayashi, Y. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 4, pp 87–120.

(9) For recent reviews on metal-mediated cycloadditions and cyclizations, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, 104, 2127. (b) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, 103, 3787. (c) Rubin, M.; Sromek, A. W.; Gervorgyan, V. *Synlett* **2003**, 2265. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, 102, 813. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, 100, 2901.

(10) For recent examples, see: (a) Sweel, R. F.; Schramm, M. P.; Kozimin, S. A. *J. Am. Chem. Soc.* **2004**, 126, 7442. (b) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, 6, 1509. (c) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, 7, 3681. (d) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, 45, 6726.

dition¹² via Brønsted or Lewis acid activation of vinyl acetals **1**¹³ en route to cyclobutane **2** or **3** (Scheme 1).

Scheme 1. Gassman's Cationic [2 + 2] Cycloaddition



Although such activations of vinyl acetals for inter- and intramolecular [4 + 2] cycloadditions¹⁴ and for oxyallyl [4 + 3] cycloadditions^{15,16} have been extensively investigated, an intramolecular variant of Gassman's cationic [2 + 2] cycloaddition employing vinyl acetals **4** tethered to an unactivated olefin for preparations of cyclobutanes **7** has not been reported. Given a number of recently isolated cyclobutane-containing natural products with biological relevance^{17,18} and that a cationic [2 + 2] cycloaddition pathway has a biosynthetic origin,¹⁹ we recognized this as an excellent opportunity to develop useful thermal [2 + 2] cycloadditions. We report here an intramolecular version of Gassman's cationic [2 + 2] cycloaddition.

To establish feasibility, we initially examined vinyl acetal **9** containing an ether tethering that was prepared from readily available 5-bromo-3-methyl-2-pentene and *cis*-2-butene-1,4-diol featuring Noyori's mild protocol for the acetal formation²⁰ (Scheme 2). The initial usage of $\text{BF}_3 \cdot \text{OEt}_2$ as Lewis acid brought forth immediate success to the proposed intramolecular cationic [2 + 2] cycloaddition, leading to cycloadduct **10**²¹ in 66% yield as a single diastereomer when using 1.0 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ along with 4 Å MS with the reaction being run in CH_2Cl_2 ²² at 0 °C for 10 min (entry 2).

(11) Also see: (a) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686. (b) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668. (c) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127. (d) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517. (e) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Nihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869. (f) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068. (g) Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919. (h) Narasaka, K.; Hayashi, Y.; Hayashi, Y. *Tetrahedron* **1994**, *50*, 4529–4542.

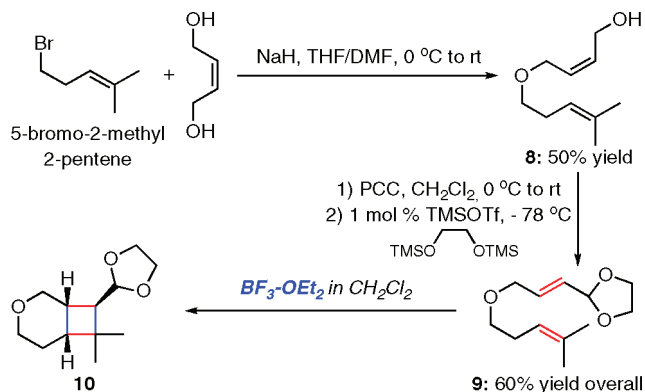
(12) (a) Gassman, P. G.; Chavan, S. P.; Fertel, L. B. *Tetrahedron Lett.* **1990**, *31*, 6489. (b) Gassman, P. G.; Lottes, A. C. *Tetrahedron Lett.* **1992**, *33*, 157.

(13) For reviews, see: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(14) For reviews, see: (a) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371. (b) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

(15) For reviews on oxyallyl cation [4 + 3] cycloadditions, see: (a) Harmata, M. *Acc. Chem. Res.* **2001**, *7*, 595. (b) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, 1998; Vol. 5, p 119. (c) West, F. G. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, p 1. (e) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (f) Harmata, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523.

Scheme 2. Gassman's Intramolecular [2 + 2] Cycloaddition



entry	equiv	concd [M]	additive	temp [°C]	time	yield [%]
1	1.0	0.005	-	0	10 min	40
2	1.0	0.005	4 Å MS	0	10 min	66
3	1.0	0.005	4 Å MS	-20	1 h	45
4	1.0	0.01	4 Å MS	0	5 min	54
5	0.5	0.005	4 Å MS	0	2 h	40
6	0.1	0.005	4 Å MS	0	12 h	5

Overall, the addition of 4 Å MS was the most critical, as its presence reduces the competing hydrolysis of the acetal moiety both in the starting vinyl acetal **9** and cycloadduct **10** (entry 1 vs 2). In addition, the reaction temperature and concentration appear to be more optimal at 0 °C and 0.005 M, respectively (entries 3 and 4). Finally, the reaction was found to be slow and sluggish when using <0.5 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ (entries 5 and 6). The relative stereochemistry of cycloadduct **10** was unambiguously established through X-ray structure of *p*-bromobenzoyl ester **12** prepared from **10** via hydrolysis and NaBH_4 reduction followed by acylation (Figure 1).

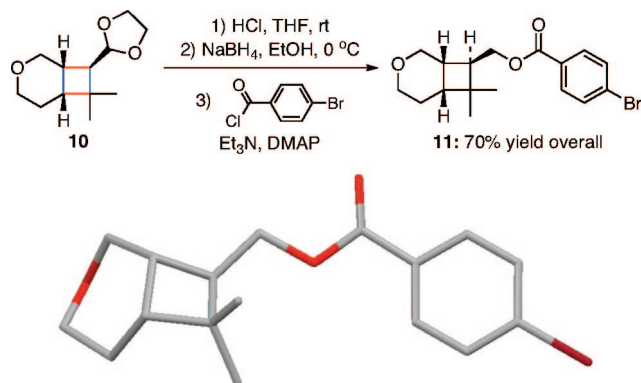


Figure 1. X-ray structure of ester **12**.

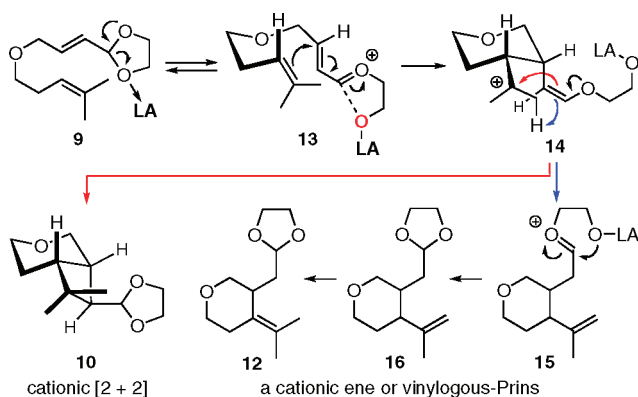
We then proceeded to evaluate other Lewis acids as well as Brønsted acids. As summarized in Table 1, SnCl_4 appears to be another useful Lewis acid (entries 3–6) and gave **10** in comparable yield when the reaction was carried out at –20 °C (entry 5). For Brønsted acids, although TfOH had

Table 1. Evaluations of Lewis and Brønsted Acids

entry	acid [equiv] ^a	concd [M] ^b	temp [°C]	time [h]	yield [%] ^c : 10
1	TMSOTf [1.0]	0.01	- 20	1	27 [40 ^d]
2	MgBr ₂ ·OEt ₂ [1.0]	0.01	- 78 to rt	10	NR ^e
3	SnCl ₄ [1.0]	0.01	- 20	10 min	48
4	SnCl ₄ [1.0]	0.005	- 78	2	NR
5	SnCl₄ [1.0]	0.005	- 20	10 min	60
6	SnCl ₄ [1.0]	0.005	0	0.5	30
7	TiCl ₄ [1.0]	0.005	- 78	2	NR
8	Tf ₂ NH [0.1]	0.005	- 78	3	34
9	Tf₂NH [1.0]	0.005	- 78	5 min	50
10	TfOH [0.1]	0.005	rt	4	10 [20 ^d]
11	MsOH [1.0]	0.005	- 78 to rt	10	NR
12	CSA or PTSA [0.2]	0.005	rt to 60	20	NR
13	TFA [1.0]	0.005	rt	48	30

^a 4 Å MS was used in all reactions except in entry 3. ^b CH₂Cl₂ was the solvent in all reactions. ^c Isolated yields. ^d A side product was isolated and identified as the half-cycloaddition product **12** (see Scheme 3). ^e NR: no reaction with full or partial recovery of the starting vinyl acetal **9**.

been found useful in Gassman's intermolecular work,¹² it was poor for our intramolecular cycloaddition (entry 10). However, HNTf₂^{23,24} was suitable for the cycloaddition (entry 9) while TFA was moderately useful (entry 13). Again, these reactions required one full equivalent of the acid and 4 Å MS. In addition, we isolated half-cycloaddition product (**12**, see Scheme 3) in 40% and 20% yield, respectively, when

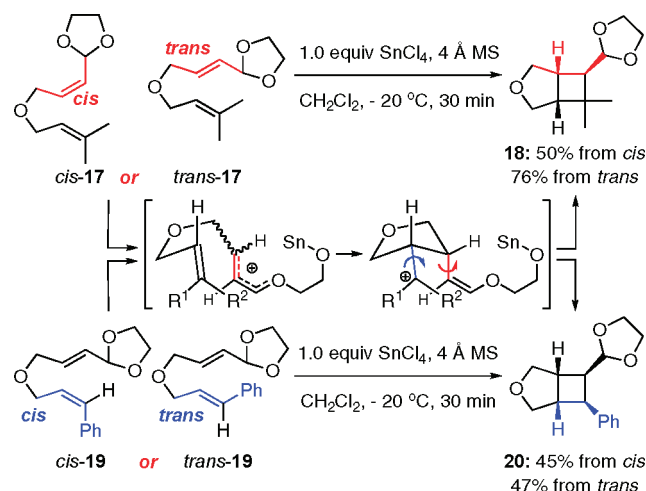
Scheme 3. [2 + 2] Versus Ene-Like Pathway

using TMSOTf and TfOH (entries 1 and 10). We note here that the nature of the acetal motif, i.e., 1,3-dioxolane used in **9** versus 1,3-dioxane,²⁵ bears no impact on the cycloaddition.

(16) For some recent examples, see: (a) Sakai, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, 23, 1693. (b) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Kashammer, D. *Chem. Ber.* **1988**, 121, 1585. (c) Murray, D. H.; Albizzati, K. *Tetrahedron Lett.* **1990**, 31, 4109. (d) Harmata, M.; Elomari, S.; Barnes, C. J. *J. Am. Chem. Soc.* **1996**, 118, 2860, and references cited within.

Having established the feasibility, we focused on some mechanistic probing and synthetic application. Mechanistically, this intramolecular [2 + 2] cycloaddition should be stepwise as illustrated in Scheme 3. The key activation of the acetal motif in **9** by Lewis Acid would give vinyl oxocarbenium ion **13** likely complexed (shown by the dashed line) to the Lewis acid coordinated oxygen (in red).²⁶ The ensuing addition of the unactivated olefin would complete the first bond formation shown in **14**. While trapping of the resulting carbocation in **14** (the red arrow) represents the desired cycloaddition pathway and the proper stereochemical course, an E1-elimination (the blue arrow) would afford alkenes **12** and **16** (not observed—if formed, it could isomerize rapidly to **12** under the reaction conditions) in a cationic ene or vinylogous-Prins manner. Alkene **12** could be derived from **14** directly via E1-elimination through an external proton scavenger or sponge.²⁷ It is noteworthy that the high level of diastereoselectivity suggests the cycloaddition proceeds through **13** with a high degree of conformational control.

To further support the stepwise nature of this cycloaddition, we prepared both *cis*- and *trans*-vinyl acetals **17** and *cis*- and *trans*-olefins **19** (Scheme 4). Cycloadditions of both

Scheme 4. *cis*- and *trans*-Vinyl Acetals

sets of isomers provided identical stereochemical outcome in the respective cycloadducts **18** and **20**. This suggests that

(17) For bielschowskysin, see: (a) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, 6, 1661. For biyouyanagin A, see: (b) Tanaka, N.; Okasaka, M.; Ishimaru, Y.; Takaishi, Y.; Sato, M.; Masato Okamoto, M.; Oshikawa, T.; Ahmed, S. U.; Consentino, L. M.; Lee, K.-H. *Org. Lett.* **2005**, 7, 2997.

(18) For an elegant approach to bielschowskysin, see: (a) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, 8, 903.

(19) For a leading reference, see: (a) Thulasiram, H. V.; Erickson, H. K.; Poulter, C. D. *Science* **2007**, 316, 73.

(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 21, 1357.

(21) See the Supporting Information.

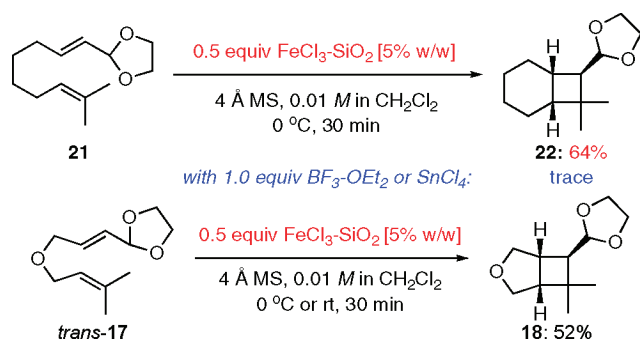
(22) Hexane and THF were examined but not useful.

(23) For a study on the acidity of HNTf₂, see: Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, 125, 5264, and references cited therein.

scrambling through these cationic intermediates (in brackets) is facile and that the stereochemical information of both the vinyl acetal and the olefin is readily lost during the stepwise pathway. It is noteworthy that the olefin stereochemistry in *cis*- or *trans*-**17** was not scrambled prior to the first bond formation. ¹H NMR of the crude mixture attained within the first 20 s of the reaction course revealed no erosion of the double-bond geometry in the unreacted *cis*- or *trans*-**17**. Likewise, the olefin in *cis*-**19** also did not isomerize under the reaction conditions.²⁸

To render this cationic [2 + 2] cycloaddition useful toward natural product synthesis, we examined vinyl acetal **21** with an all-carbon tether. As shown in Scheme 5, the

Scheme 5. Fused Carbocyclic Systems

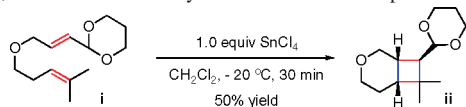


reaction of **21** behaved differently, as neither $\text{BF}_3 \cdot \text{OEt}_2$ nor SnCl_4 was useful in promoting this cycloaddition. After much screening, 0.5 equiv of FeCl_3 adsorbed on activated silica gel (5% w/w)²⁹ was found to be the most optimal Lewis acid at 0 °C to give the desired cycloadduct **22** in 64% yield, although neither SiO_2 nor 0.1 equiv of FeCl_3 alone at 0 °C to rt afforded any desired product. On the other hand, *trans*-vinyl acetal **17** with the oxygen atom-containing tether could also undergo cycloaddition in a comparable yield when using 0.5 equiv of $\text{FeCl}_3\text{-SiO}_2$. We are currently investing this intriguing comparison.³⁰

Having established this new protocol for cycloaddition of a vinyl acetal containing an all-carbon tether, we pursued an application of this reaction in formal total syntheses of

(24) Ko, C.; Hsung, R. P. *Organic Biomol. Chem.* **2007**, 7, 431.

(25) 1,3-Dioxane based vinyl acetal **i** led to a comparable outcome.



(26) (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (b) Alexakis, A.; Mangeney, P. *Tetrahedron Asymmetry* **1990**, 1, 477.

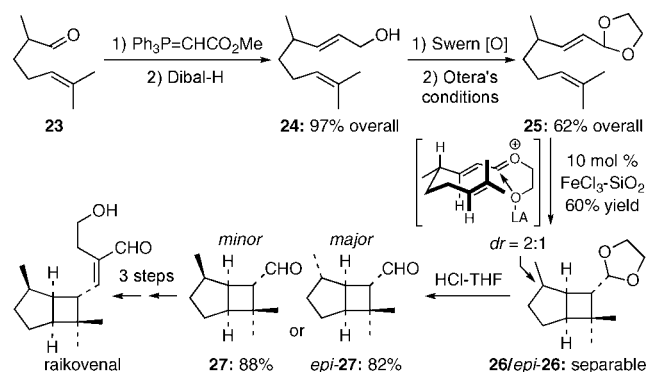
(27) In response to an excellent suggestion by a reviewer, with 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine, it gave 55% yield of **10** when using SnCl_4 with no changes in the yield of alkene **12** (or **16**).

(28) The crude reaction mixture from *cis*-**19** was analyzed within the first 5 s, and the ratio of unreacted *cis*-**19**/**20** was 2:1. The reaction of *trans*-**19** was too fast and completed within 5 s. Thus, it was inconclusive in assessing the integrity of olefin stereochemistry in this case. We are again grateful for the reviewers' insightful suggestions.

(29) For a preparation of $\text{FeCl}_3\text{-SiO}_2$, see: (a) Chavan, S. P.; Sharma, A. K. *Synlett* **2001**, 667.

raikovenal and *epi*-raikovenal.^{31,32} The key vinyl acetal **25** could be constructed from δ -enal **23** in four steps featuring Otera's conditions for the vinyl acetal formation (Scheme 6).³³ Again, constructing the acetal motif in these all-carbon

Scheme 6. Formal Synthesis of Raikovenal



tethered vinyl acetals [including **21**] was also surprisingly different, as Noyori's protocol was not useful. The ensuing cycloaddition gave the desired cyclobutane **26** and *epi*-**26** in 60% yield as a separable isomeric mixture with a ratio of 2:1 in favor of *epi*-**26**. Chromatographic separation and hydrolysis gave aldehydes **27** and *epi*-**27** for which both spectroscopically matched the reported literature values.³² NOE experiments of **26** and *epi*-**26** also confirmed their respective relative stereochemistry. The major isomer *epi*-**26** is likely a result of the cycloaddition proceeding through the more favored conformation shown in brackets.

We have described Gassman's intramolecular cationic [2 + 2] cycloaddition of vinyl acetals tethered to an unactivated olefin and its application in formal syntheses of raikovenal and *epi*-raikovenal.

Acknowledgment. We thank ACS-PRF-AC and UW-Madison for funding. We thank Dr. Vic Young and Ben Kucera at the University of Minnesota for providing X-ray structural analysis.

Supporting Information Available: Experimental procedures as well as ¹H NMR spectral and characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(30) Preliminarily, cycloadditions of vinyl acetals with nitrogen atom-containing tethers could also be accomplished in a comparable manner using SnCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, or $\text{FeCl}_3\text{-SiO}_2$.

(31) For isolation, see: (a) Guella, G.; Dini, F.; Erra, F.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2585. (b) Guella, G.; Dini, F.; Pietra, F. *Helv. Chim. Acta* **1995**, 78, 1747.

(32) For total syntheses, see: (a) Snider, B.; Lu, Q. *Synth. Commun.* **1997**, 27, 1583. (b) Rosini, G.; Laffi, F.; Marotta, E.; Pagani, I.; Righi, P. *J. Org. Chem.* **1998**, 63, 2389.

(33) Conditions: 2.0 equiv of MgSO_4 , 10 mol % of $\text{HOBu}_2\text{SnOSnBu}_2\text{NCS}$, 20 equiv of $\text{HOCH}_2\text{CH}_2\text{OH}$, benzene, 80 °C, 48 h. See: Otera, J.; Dan-Oh, N.; Nozaki, H. *Tetrahedron* **1992**, 48, 1449.