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Regioselective Tandem Dimethylsulfonium Methylide Addition–Eliminative Olefination of Diendioates: A Novel Route to 1,3-Butadien-2-ylmalonates

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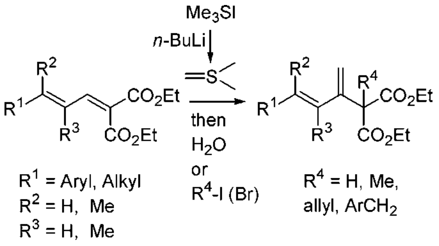
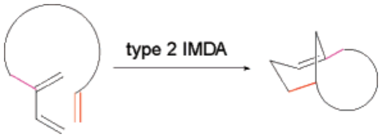
ABSTRACT



The appropriate choice of dimethylsulfonium methylide generation conditions enables the highly regioselective tandem ylide addition–eliminative olefination to 1,3-dienedioates providing 1,3-butadien-2-ylmalonates, a novel class of 2-substituted 1,3-dienes suitable for quick assembly of precursors for type 2 intramolecular Diels–Alder reactions.

Bicyclo[n.3.1] alkenes with multiple functionalities and a bridgehead double bond are useful intermediates, notably for the synthesis of taxoids,[1] phomoidrides[2] (CP molecules), and other classes of natural products.[3] The type 2 intramolecular Diels−Alder (T2IMDA) reaction[4] (Scheme 1) is one of the few direct methods[5] that provide bridged bicyclic rings, incorporating a bridgehead double bond[6] (*anti*-Bredt olefin).

Scheme 1



For T2IMDA, the dienophile component is attached to the 2 position of the 1,3-diene with an appropriate tether. For this, 1,3-butadienes substituted with suitable functionality at the 2 position are a prerequisite that would enable the

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[1] (a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327. (b) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665−667. (c) Kingston, D. G. I. *Chem. Commun.* **2001**, 867−880. (d) Nicolaou, K. C.; Dai, W-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (f) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

[2] (a) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594−1598. (b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1−7. (d) Starr, J. T.; Carriera, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415−1421. (e) Spiegel, D.; Andarson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691−2727.

[3] Selected references: (a) Zhu, L.; Lauchli, R.; Loo, M.; Shea, K. J. *Org. Lett.* **2007**, *9*, 2269−2271. (b) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287−5289. (c) Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea, K. J. *J. Org. Chem.* **2004**, *69*, 3025−3035. (d) Whitney, J. M.; Parnes, J. S.; Shea, K. J. *J. Org. Chem.* **1997**, *62*, 8962−8963. (e) Dzierba, C. D.; Zandi, K. S.; Mollers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711−4712.

[4] Recent reviews: (a) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779−4807. (b) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820−849. (c) Rappoport, Z. *The Chemistry of Dienes and Polyenes*; John Wiley and Sons: New York, 2001; Vol. 2 and references therein.

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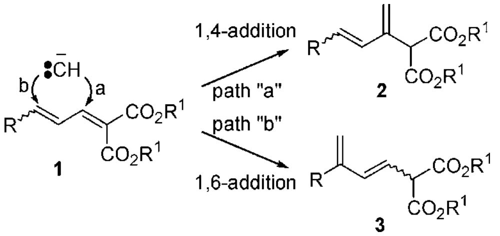
attachment of the dienophile fragment. Moreover, 2-substituted 1,3-butadienes are an integral part of many natural products.[7] This has resulted in the development of a number of methods for their preparation.[8−11] Many of these methodologies involve organometallic species such as 1,3-butadienyl-2-metal[9] or 2,3-butadienyl-1-metal,[10] which often suffer from poor regioselectivity or low yield and, in some cases, require starting materials that are not readily accessible. More recently, attractive alternative methods such as Barbier-type coupling[8,11c] and ethylene-alkyne cross-metathesis[11b,d] have been reported for their preparation. However, although efficient, few methods are applicable to the synthesis of 2-substituted 1,3-butadienes where a quick assembly of a dienophile fragment can be made to perform T2IMDA.

We envisage that the nucleophilic addition of a carbene anion equivalent[12] to an activated 1,3-diene **1** (Scheme 2) would provide a solution to this. Depending on the regio- and stereoselectivity of the addition, four isomeric 2-substituted 1,3-diene products, *E* and *Z* **2**, **3**, can be formed.

Scheme 2



As a continuation of our work on developing new methodologies using dimethylsulfonium methylide **4**,[13,14] we have recently reported[15] an interesting observation that **4** in combination with a base, such as sodium dimsylate, undergoes a tandem ylide addition−eliminative olefination on various activated olefins and thus acts as an equivalent of a carbene anion. This strategy has been used in sequential tandem olefination−alkylation for the preparation of 1-substituted vinyl silanes, styrenes, and products derived from them.[16] The methodology has been extended for sequential tandem double olefination of vinyl phosphonates and aldehydes to provide di- and tri-substituted 1,3-dienes with very high regio- and stereoselectivity.[17] We were curious to know whether this novel olefination is applicable to extended conjugated systems such as 1,3-diendioates **1** and if so, which of the two regioisomeric dienic products **2** or **3** (Scheme 2) would dominate. Although, the conjugate addition[18] of carbon or heteroatomic nucleophilic reagents to activated olefins is a highly useful reaction in organic synthesis, the regioselectivity issue, namely, 1,4-addition versus 1,6-addition,[19−22] sometimes becomes challenging to extended conjugated systems. We report herein the first example of tandem 1,4-addition−elimination of ylide **4** to 4-aryl/alkyl-substituted 1,3-diendioates **1** to give 1,3-butadien-2-ylmalonates **2**, a

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(5) Selected examples of recent approaches to the bridgehead alkene, see: (a) Mehta, G.; Kumaran, R. S. *Chem. Commun.* **2002**, 1456−1457. (b) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157−2158. (c) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714−2715. (d) Cossy, J.; BouzBouz, S.; Laghgar, M.; Tabyaoui, B. *Tetrahedron Lett.* **2002**, *43*, 823−827. (e) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215−5218. (f) Yoshimitsu, T.; Yanagisawa, S.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751−3754. (g) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431−2434. (h) Kaliappan, K. P.; Ravikumar, V.; Pujari, S. A. *Tetrahedron Lett.* **2006**, *47*, 981−984.

(6) Reviews on *anti*-Bredt alkenes and their reactivities: (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683−1715. (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067−1093. (c) Marshall, J. A.; Faubl, H. *J. Am. Chem. Soc.* **1967**, *89*, 5965−5966. (d) Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966−5968. (e) Wiseman, J. R.; Chong, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 7775−7777.

(7) (a) Shen, Y.-C.; Wang, L.-T.; Wang, C.-H.; Khalil, A. T.; Guh, J.-H. *Chem. Pharm. Bull.* **2004**, *52*, 108−110. (b) Prakash, C. V. S.; Hoch, J. M.; Kingston, D. G. I. *J. Nat. Prod.* **2002**, *65*, 100−107. (c) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Chem. Lett.* **2001**, *9*, 1911−1921.

(8) (a) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925−1928. (b) Bloch, R.; Chaptal-Gradoz, N. *J. Org. Chem.* **1994**, *59*, 4162−4169. (d) Patel, R. M.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 4900−4904. (e) Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2006**, 2463−2483. (f) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493−2498 and references therein.

(9) (a) Luo, M.; Iwabuchi, Y.; Hatakeyama, S. *Synlett* **1999**, 1109−1111. (b) Nativi, C.; Taddei, M. *Tetrahedron* **1989**, *45*, 1131−1144. (c) Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1129−1131. (d) Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1942−1945. (e) Nunomoto, S.; Yamahita, Y. *J. Org. Chem.* **1979**, *44*, 4788−4791.

(10) (a) Yu, C.-M.; Lee, S.-J.; Jeon, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3557−3558. (b) Luo, M.; Iwabuchi, Y.; Hatakeyama, S. *Chem. Commun.* **1999**, 267−268. (c) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100−104.

(11) (a) Phukan, P.; Bauer, M.; Maier, M. E. *Synthesis* **2003**, 1324−1328. (b) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788−1792. (c) Lu, W.; Ma, J.; Yang, Y.; Chan, T. H. *Org. Lett.* **2000**, *2*, 3469−3471. (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. (e) Katritsky, A. R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* **1999**, *64*, 1888−1892. (f) Yu, C.-M.; Yoon, S.-K.; Lee, S.-J.; Lee, J.-Y.; Kim, S. *Chem. Commun.* **1998**, 2749−2750.

(12) For the use of this terminology, see: Cohen, T.; Yu, L. C. *J. Org. Chem.* **1984**, *49*, 605−608.

(13) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(14) For other uses of **4**, see: Alcaraz, L.; Cox, K.; Cridland, A. P.; Kinchin, E.; Morris, J.; Thompson, S. P. *Org. Lett.* **2005**, *7*, 1399−1401 and references therein.

(15) (a) Date, S. M.; Singh, R.; Ghosh, S. K. *Org. Biomol. Chem.* **2005**, *3*, 3369−3378. (b) Ghosh, S. K.; Singh, R.; Date, S. M. *Chem. Commun.* **2003**, 636−637.

(16) (a) Singh, R.; Singh, G. C.; Ghosh, S. K. *Tetrahedron Lett.* **2005**, *46*, 4719−4722. (b) Singh, R.; Singh, G. C.; Ghosh, S. K. *Eur. J. Org. Chem.* **2007**, 5376−5385. (c) Ghosh, S. K.; Singh, R.; Singh, G. C. *Eur. J. Org. Chem.* **2004**, 4141−4147.

(17) (a) Date, S. M.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 386−388. (b) Date, S. M.; Ghosh, S. K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2099−2100.

(18) Reviews: (a) Lipshutz, B.H.; Sengupta, S. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1992; Vol. 41, pp 135−631. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(19) Selected examples of Cu catalyzed addition: (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119−126. (b) Barbot, F.; Kadib-Elban, A.; Miginiac, P. *Tetrahedron Lett.* **1983**, *24*, 5089−5090. (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019−6022. (d) Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* **1983**, *255*, 1−9. (e) Uerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799−2804. (f) Liu, H.; Gayo, L. M.; Sullivan, R. W.; Choi, A. Y. H.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 3284−3288. (g) Modi, S. P.; Gardner, J. O.; Milowsky, A.; Wierzba, M.; Forgione, L.; Mazur, P.; Solo, A. J.; Duax, W. L.; Galdecki, Z.; Grochulski, P.; Wawrzak, Z. *J. Org. Chem.* **1989**, *54*, 2317−2321. (h) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186−204.

(20) Iron-catalyzed addition: (a) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603−606. (b) Furstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624−629.

(21) Rh^{I}-catalyzed addition: (a) Hayahi, T.; Yamamoto, S.; Tokugana, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224−4227. (b) Herran, G. de la; Murcia, C.; Csaky, A. G. *Org. Lett.* **2005**, *7*, 5629−5632.

(22) Silicon and tin reagents: Krief, A.; Dumont, W.; Provins, L. *Synlett* **1995**, 121−122.

novel class of dienes with a functionality at the 2 position amenable for further maneuvering and/or quick lodging of a dienophile fragment.

When 4-phenyl dienedioate **1a** was added to ylide **4**, generated using Me_3SI and sodium dimsylate in DMSO−THF under the reported conditions,[15] we obtained a mixture of diene **2a**, vinylcyclopropane **5a**, and the thiomethyl product **6a** (**2a**/**5a**/**6a** = 50:20:30) (Scheme 3). Although the formation of the cyclopropane **5a** could be curbed (Table 1) by varying the stoichiometry of the reactants, the formation of product **6a**[23] could not be minimized. Therefore, we modified[16b] the generation of ylide **4** by using *n*-BuLi in THF instead of sodium dimsylate.[24] When this modified procedure was implemented in the reaction of **1a** with **4**, the dienic product **2a** was formed in very good yield (96%) (Scheme 4). The reaction was highly regioselective, and the dienic product **3** could not be detected as 1,6-addition of ylide **4** did not take place. Moreover, if the reaction was quenched with MeI (5 equiv) before workup, methylated product **7a** was obtained in 87% yield.[25]

Scheme 3

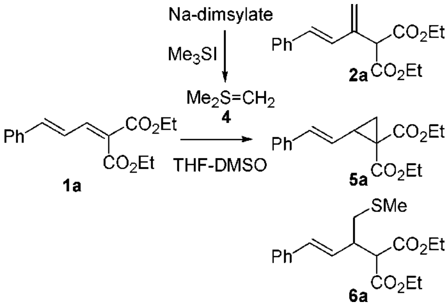
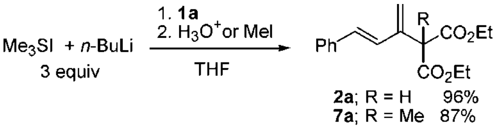


Table 1. Tandem Addition−Eliminative−Olefination on **1a** Mediated by Me_3SI and Na-Dimsylate

entry (equiv)	Na-dimsylate	Me_3SI (equiv)	**2a**:**5a**:**6a**[a]
1	2.5	1.2	50:20:30
2	3	1.5	74: −[b]:26
3	4	2.5	78: −[b]:22
4	3	3	45:30:25

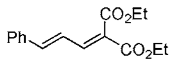
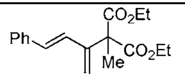
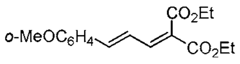
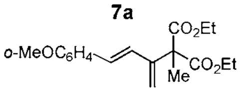
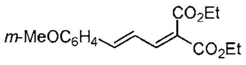
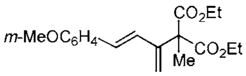
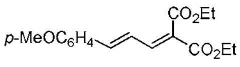
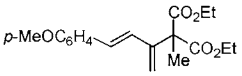
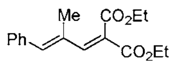
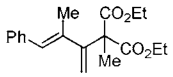
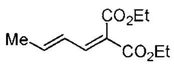
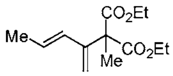
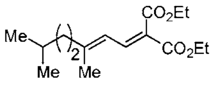
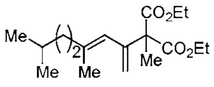
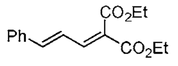
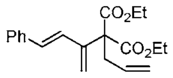
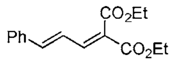
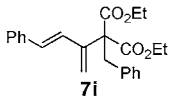
[a] Determined from crude product by ^1H NMR. [b] Peaks for **5a** could not be seen.

Scheme 4



This reaction was found to be general and independent of a substituent such as a OMe group present in the aryl ring, as well as a substituent such as Me group at position 3 of the diendioates **1**. The diesters **1b**−**e** were prepared by Knoevenagel condensation of the corresponding substituted cinnamaldehydes with diethyl malonate. When these substrates were reacted with ylide **4**, the desired products **7b**−**e** were isolated in good yields after methylation (Table 2). The substituent at position 4 of the diene **1** may not need to be an aryl group; for example, Me in diene **1f** and Me and an alkyl group in **1g** also gave the desired methylated products **7f** and **7g**, respectively. The stereochemistry of the double bond at the γ,δ position remained unaffected during the process. The (*E*)-stereochemistry of this double bond in

Table 2. Sequential Tandem Sulfonium Ylide Addition−Eliminative Olefination−Alkylation of Diendioates **1**

entry	substrate	product	yield (%)[a]
1	 **1a**	 **7a**	87
2	 **1b**	 **7b**	81
3	 **1c**	 **7c**	88
4	 **1d**	 **7d**	85
5	 **1e**	 **7e**	78
6	 **1f**	 **7f**	68
7	 **1g**	 **7g**	65
8	 **1a**	 **7h**	83[b]
9	 **1a**	 **7i**	81[c]

[a] Isolated yield. [b] 3 equiv each of K_2CO_3 and allyl bromide were used. [c] 3 equiv each of K_2CO_3 and benzyl bromide were used.

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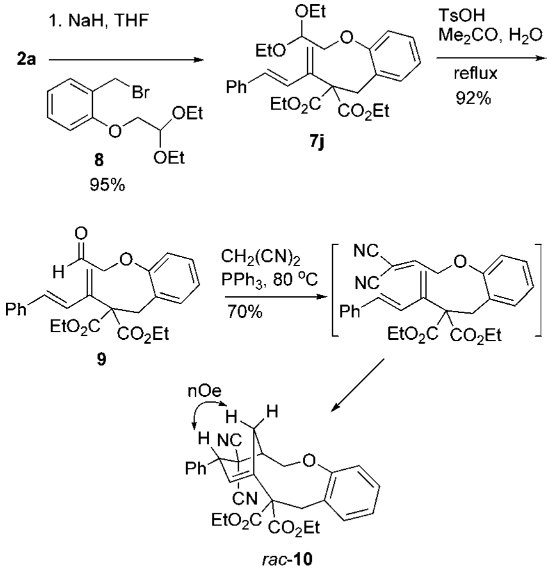
(23) Compounds **6a** and **2a** were unseparable; **6a** was characterized after methylation.

(24) Caution! Na-Dimsylate is known for its explosive nature.

products **7a**−**d** was assigned from the ^{1}H coupling constants ($J \approx 16$ Hz). The starting dienes **1e** and **1g** were contaminated with 18% and 35% of the (Z)-isomer, respectively. Thus the products **7e** and **7g** were also contaminated with the isomeric product in the same proportions. When the reaction between **1a** and ylide **4** was quenched with 3 equiv of allyl and benzyl bromides, the corresponding alkylated products **7h** (74%) and **7i** (53%) were isolated. The yields were improved (Table 2; entries 8 and 9) by adding anhydrous K_2CO_3 into the reaction mixture prior to addition of bromides.

By quenching the reaction with a suitable alkyl halide that has the desired tether length and an in-built dienophile or has the capability to provide one, the system would be ideally suited for T2IMDA. The cycloadduct from T2IMDA reaction would be the bicyclo[*n*.3.1] alkene with a bridgehead double bond, and the size of the bridge would depend upon the tether length. As a model study, the olefination product **2a** was deprotonated using sodium hydride and reacted with the substituted benzyl bromide **8**,[26] which provided the alkylated diene **7j** in excellent yield (Scheme 5). The acetal group in **7j** was hydrolyzed, and the resulting aldehyde **9** was subjected to Knoevenagel condensation with malononitrile catalyzed by triphenylphosphine[27] under solvent-free condition at 80 °C. Interestingly, a domino[28] Knoevenagel−T2IMDA sequence provided the bridged bicyclic product *rac*-**10** in good yield. The stereochemical feature of *rac*-**10** was determined by COSY and ROESY analysis and was further confirmed by X-ray crystallography[29] as shown in Figure 1.

Scheme 5



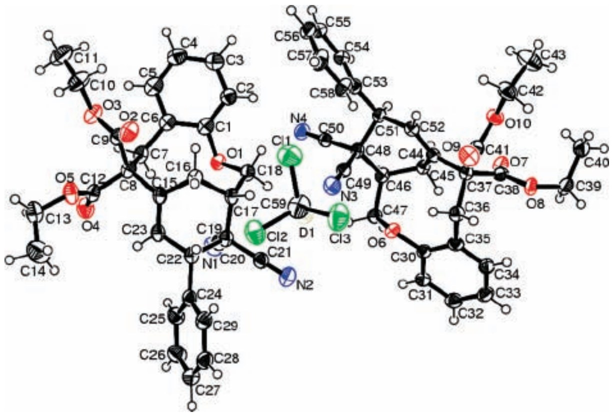


Figure 1. ORTEP plot of two molecules of *rac*-**10** + $CDCl_3$.

In summary, we have developed a novel and operationally simple regio- and stereoselective synthesis of 2-functionalized 1,3-butadienes from readily accessible activated 1,3-dienes using dimethylsulfonium methylide. This led to the synthetically valuable intermediates suitable for quick assembly of dienophiles thus ready for a T2IMDA. The ability of this methodology has been demonstrated by synthesizing a bicyclo[6.3.1] dodecene skeleton efficiently in a domino Knoevenagel−T2IMDA sequence with excellent stereocontrol.

Acknowledgment. We are grateful to the National Single-Crystal X-ray Diffraction Facility at IIT Bombay for the crystallographic results.

Supporting Information Available: Typical experimental procedure, full characterization data, copies of ^{1}H and ^{13}C NMR, and X-ray single-crystal data for *rac*-**10** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) To a −10 °C suspension of Me_3SI (3 mmol) in THF (3 mL) was added *n*-BuLi (3 mmol, 1.6 M hexane solution). After 20 min, diendioate **1** (1.0 mmol) in THF (3 mL) was introduced, and the reaction was slowly allowed to warm to room temperature. After 1 h, the reaction mixture was cooled, and methyl iodide (5 mmol) was added and stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using hexane/ethyl acetate to give the dienes **7**.

(26) Synthesis of **8** has been achieved from *o*-cresol. See Supporting Information.

(27) Yadav, J. S.; Reddy, B. V. S; Basak, A. K.; Boddapati, V.; Narsaiah, A. V.; Nagaiah, K. *Eur. J. Org. Chem.*, **2004**, 546−551.

(28) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

(29) Selected X-ray crystallographic data: $C_{59}H_{56}Cl_3DN_4O_{10}$ (corresponds to two molecules of **10** + $CDCl_3$ in the unit cell); $M = 1089.44$; triclinic, P-1; $a = 12.1477(10)$ Å, $b = 15.0735(8)$ Å, $c = 17.2611(15)$ Å, $\beta = 100.049(7)$, $V = 2718.4(4)$ Å^3, $Z = 2$, $D_{calcd} = 1.331$ g cm^{-3}, $\mu = 0.232$ mm^{-1}. Reflections collected: unique: 22688/9454 [R(int) = 0.0314]; final R indices [$I > 2\sigma(I)$]: R1 = 0.0578, wR2 = 0.1565; R indices (all data), R1 = 0.0801, wR2 = 0.1703.