Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4227-4230, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0754-L

First Enantioselective Synthesis of Mikanecic Acid via Diels–Alder Cycloaddition Mediated Construction of Chiral Vinylic Quaternary Center

Deevi Basavaiah,* Subramanian Pandiaraju and Pakala K.S. Sarma

School of Chemistry, University of Hyderabad, Hyderabad 500 134, India.

Abstract: Chiral mikanecic acid (1) was synthesized in 74% enantiomeric purity (92% ee after crystallization) *via* asymmetric Diels-Alder reaction of a novel *in situ* generated chiral 1,3-butadiene-2-carboxylate (A).

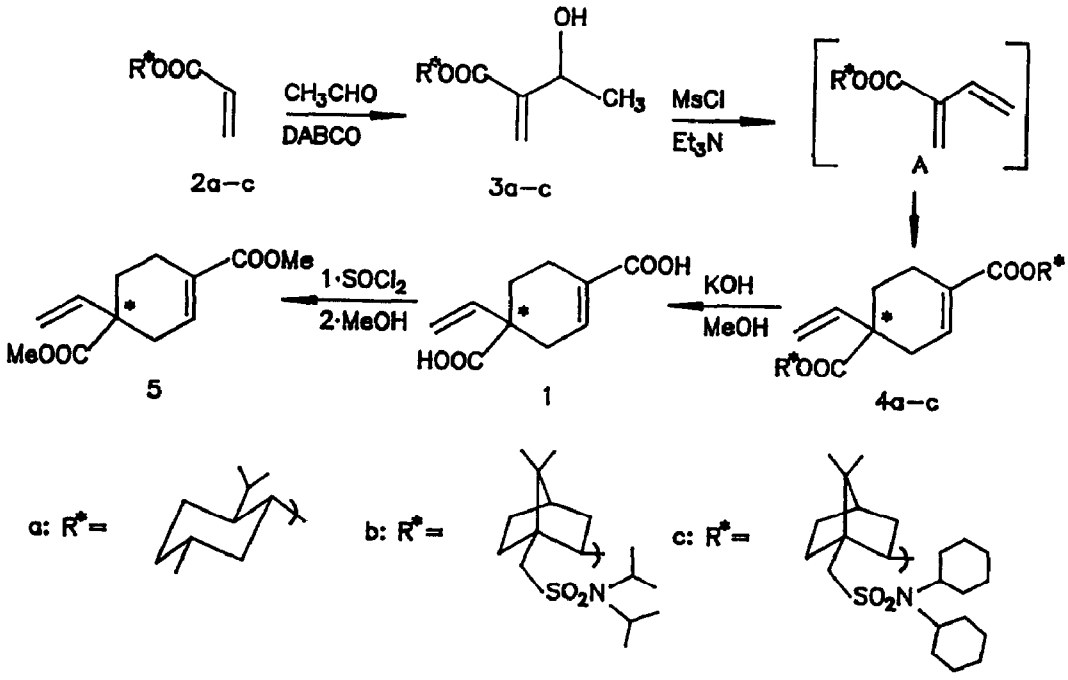
Construction of chiral quaternary carbon center(s) has been one of the challenging and attractive areas in synthetic organic chemistry because a number of biologically active natural products contain such structural subunits.[1]

Mikanecic acid (1), a terpene dicarboxylic acid, has attracted our attention owing to its special feature of having a vinylic quaternary carbon center in a functionalized six membered cyclic system.[2] Mikanecic acid was isolated in 1936 by Manske[3] from the products of alkaline hydrolysis of the alkaloid mikanoidine obtained from *Senecio mikanioides* Otto. In the intervening years several reports have appeared regarding the history,[4] characterization[2] and synthesis of racemic mikanecic acid.[5] Hoffmann and Rabe[5a] reported the synthesis of racemic mikanecic acid using a Baylis-Hillman adduct *via* Diels-Alder reaction. However, to the best of our knowledge, there has been no report in the literature on optically active mikanecic acid. Herein, we disclose the first enantioselective synthesis of mikanecic acid *via* double stereodifferentiating[6] asymmetric Diels-Alder cycloaddition of a novel, chiral 1,3-butadiene-2-carboxylate (A), generated *in situ*, as both a chiral diene and chiral dienophile.

Although the Diels-Alder reaction is undoubtedly one of the corner-stones of organic chemistry, very few examples have been documented for the construction of chiral quaternary carbon centers and these demonstrate a number of practical difficulties.[7] In recent years there has been increasing interest in the Baylis-Hillman reaction because this reaction provides synthetically useful multifunctional molecules.[8-10] Our recent work[11] on this reaction led us to consider utilizing the Baylis-Hillman

adduct, obtained via the coupling of acetaldehyde and suitable chiral acrylate, as an appropriate starting material for the *in situ* generation of a novel, chiral 1,3-butadiene-2-carboxylate (**A**). This would be expected to undergo spontaneous double stereodifferentiating Diels-Alder reaction to provide, after hydrolysis, the desired optically active mikanecic acid (**1**). Accordingly, we have selected the three chiral acrylates **2a**, **2b** and **2c** for our studies[12] (Scheme 1).

Scheme 1:



Baylis-Hillman adducts **3a-c**, obtained via the coupling of chiral acrylates **2a-c** with acetaldehyde in the presence of 1,4-diazabicyclo(2.2.2)octane (DABCO), on treatment with $MsCl/Et_3N$ led directly to the formation of mikanecic acid diesters **4a-c**, through Diels-Alder reaction of the *in situ* generated chiral 1,3-butadiene-2-carboxylate (**A**). Hydrolysis of these diesters **4a-c** with KOH/MeOH provided the desired regiomerically pure optically active mikanecic acid in 25%, 69% and 74% enantiomeric purities respectively (Table 1).

The following procedure for the synthesis of **4c** is representative. To a solution of **3c**[13] (2.89 g, 5.85 mM) in methylene chloride (4 mL) at $0^{o}C$ was added a solution of mesyl chloride (0.45 mL, 5.85 mM) in methylene chloride (2 mL) followed by dropwise addition of a solution of triethylamine (3.26 mL, 23.4 mM) in methylene chloride (4 mL). The

Table 1: Enantioselective synthesis of mikanecic acid (1) from chiral acrylates 2a-c.

Chiral acrylate	Mikanecic acid[a]		
	Overall yield (%)[b]	$[\alpha]_D^{22}$	ee(%)[c]
2a	51	-3.30 (c 1.74, acetone)	25
2b	40	+8.62 (c 0.96, acetone)	69
2c	39	+9.17 (c 0.43, acetone)	74[d]

(a) Mikanecic acid prepared from chiral acrylates **2a-c** gave satisfactory spectral analysis. (b) Overall yield based on chiral acrylate. (c) Unequivocally determined by the HPLC analysis of dimethyl ester of mikanecic acid using a CHIRALCEL OD column using 2% i-PrOH in hexane and comparison with a racemic analogue.[14] (d) A single crystallization of the compound **4c** with 25% benzene in hexane afforded, after hydrolysis, (+)-mikanecic acid, m.p: 233-235°C, $[\alpha]_D^{22}$: +11.21 (c 0.33, acetone) with 92% enantiomeric excess.

reaction mixture was stirred at 0°C for one hour and at room temperature for four hours. Usual workup followed by column chromatography (2% ethyl acetate in hexane) afforded **4c**[15] in 75% yield (2.1 g), m.p: 202-204°C, $[\alpha]_D^{22}$: -59.83 (c 0.72, acetone).

Preparation of mikanecic acid (1): The compound **4c** (0.6 g, 0.63 mM) was hydrolyzed with KOH/MeOH at room temperature for 12 hours to provide (+)-mikanecic acid (1)[16] in 69% (0.085 g) yield after usual workup (m.p: 236-238°C (lit[5b] m.p. of racemic sample: 239-240°C), $[\alpha]_D^{22}$: +9.17 (c 0.43, acetone). The enantiomeric excess was determined by the HPLC analysis of dimethyl ester[17] of this acid, which was prepared by treatment with thionyl chloride followed by methanol.

In conclusion, our method represents an indirect way of performing a double stereodifferentiating asymmetric Diels-Alder reaction involving the same molecule as chiral diene and chiral dienophile generated *in situ* thus demonstrating the synthetic potentiality of the Baylis-Hillman reaction leading to enantioselective synthesis of mikanecic acid.

Acknowledgements: We thank CSIR (New Delhi) for funding this project. S.P. thanks UGC (New Delhi) and P.K.S.S. thanks CSIR (New Delhi) for financial assistance. We thank the UGC (New Delhi) for the special assistance programme in organic chemistry and COSIST programme in Organic Synthesis in the School of Chemistry, University of Hyderabad.

References and Notes:

1. Fuji, K. *Chem. Rev.*,1993, 93, 2037-2066.
2. Culvenor, C.C.J.; Geissman,T.A. *Chem and Ind.*, 1959, 366-367.
3. Manske, R.H.F. *Canad. J. Res.*, 1936, 14B, 6-11.
4. Sydnes, L.K.; Skattebol, L.; Chapleo, C.B.; Leppard, D.G.; Svanholt K.L.; Dreiding, A.S. *Helv. Chim. Acta.* 1975, 58, 2061-2073 and references cited therein.
5. (a) Hoffmann, H.M.R.; Rabe, J. *Helv. Chim. Acta.* 1984, 67, 413-415. (b) Baraldi, P.G.; Barco, A.; Benetti, S.; Manfredini, S.; Pollini, G.P.; Simoni, D.; Zanirato, V. *Tetrahedron*, 1988, 44, 6451-6454. (c) Goldberg, O.; Dreiding, A.S. *Helv. Chim. Acta*, 1976, 59, 1904-1910.
6. Masamune, S.; Choy, W.; Peterson, J.S.; Sita, L.R. *Angew. Chem. Int. Ed. Engl.* 1985, 24, 1-30.
7. (a) Furuta, K.; Shimizu, S.; Miwa,Y.; Yamamoto, H. *J. Org. Chem.*, 1989, 54, 1481-1483. (b) Boeckman, Jr.R.K.; Nelson, S.G.; Gaul, M.D. *J. Am. Chem. Soc.*, 1992, 114, 2258-2260. (c) Masamune, S.; Reed, L.A.; Davis, J.T.; Choy, W. *J. Org. Chem*, 1983, 48, 4441-4444. (d) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.*, 1988, 110, 1238-1256.
8. Drewes, S.E.; Roos, G.H.P. *Tetrahedron*, 1988, 44, 4653-4670.
9. Basavaiah, D.; Gowriswari, V.V.L. *Tetrahedron Lett.* 1986, 27, 2031-2032.
10. Fort, Y.; Berthe, M.C.; Caubere, P. *Tetrahedron*, 1992, 48, 6371-6384.
11. Basavaiah, D.; Gowriswari, V.V.L.; Sarma, P.K.S.; Rao, P.D. *Tetrahedron Lett.* 1990, 31, 1621-1624.
12. The acrylates 2b and 2c were prepared from Oppolzer's chiral auxiliaries. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.*, 1984, 25, 5885-5888.
13. The reaction of 2c (1 equiv.) with acetaldehyde (excess) in the presence of DABCO (1 equiv.) at room temperature for 4 days provided 3c in 76% yield.
14. Dimethyl ester of racemic mikanecic acid was prepared in 85% yield from methyl 3-hydroxy-2-methylenebutanoate and $MsCl/Et_3N$ in CH_2Cl_2.
15. **Spectral data for 4c:** ^1H NMR (200 MHz) ($CDCl_3$): δ 0.82-3.41 (m, 80H), 4.82-5.26 (m, 4H), 5.72-5.98 (m, 1H), 6.88 (m, 1H); ^{13}C NMR (50 MHz) ($CDCl_3$): δ 20.09, 20.19, 20.52, 21.70, 25.20, 26.52, 27.07, 30.09, 30.18, 30.67, 31.86, 32.33, 32.68, 33.03, 33.38, 39.76, 44.38, 44.51, 47.11, 49.16, 49.46, 49.52, 53.72, 53.85, 57.50, 57.54, 78.29, 79.35, 115.72, 130.13, 136.21, 138.45, 165.16, 173.10; IR: ν_{max}/cm^{-1} (KBr): 1705, 1635.
16. **Spectral data for 1:** ^1H NMR (200 MHz) ($DMSO-d_6$): 1.67-2.82 (m, 6H), 5.02-5.28 (m, 2H), 5.76-6.02 (m, 1H), 6.85 (m, 1H), 12.42 (br s, 2H); IR: ν_{max}/cm^{-1} (KBr): 3300-2600, 1690, 1640.
17. **Spectral data for 5:** ^1H NMR (200 MHz) ($CDCl_3$): δ 1.72-1.92 (m, 1H), 2.04-2.18 (m, 1H), 2.28-2.44 (m, 3H), 2.72-2.92 (m, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 5.02-5.20 (m, 2H), 5.78-5.98 (m, 1H), 6.97 (m, 1H); ^{13}C NMR (50 MHz) ($CDCl_3$): δ 21.71, 29.46, 32.17, 47.21, 51.47, 52.16, 115.10, 129.37, 136.90, 139.41, 167.20, 174.68 (^{13}C NMR indicates the absence of any regioisomer); IR: ν_{max}/cm^{-1} (neat): 1710, 1640.

(*Received in UK* 18 *February* 1994; *revised* 7 *April* 1994; *accepted* 15 *April* 1994)