Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1723–1728

TETRAHEDRON: *ASYMMETRY*

Chiral 3-(hydroxymethyl)oxiranecarboxylic acids via the Jocic reaction

James E. Oliver [a,*] and Walter F. Schmidt [b]

[a] *Insect Chemical Ecology Laboratory, Agricultural Research Service, US Department of Agriculture, Beltsvile, MD 20705-2350, USA*

[b] *Environmental Chemistry Laboratory, Agricultural Research Service, US Department of Agriculture, Beltsvile, MD 20705-2350, USA*

Received 10 March 1998; accepted 30 March 1998

Abstract

(*R*,*R*)-2,2-Dimethyl-α-(trichloromethyl)-1,3-dioxolane-4-methanol **5** and its (*R*,*S*)-isomer **6** were converted into the TBDMS ethers of (2*S*,3*R*)-methyl 3-(hydroxymethyl)oxiranecarboxylate **12** and its (2*R*,3*R*)-isomer **14**, respectively, with 100% stereoselectivity. *threo*-Glycols afforded *cis*-epoxides, while *erythro*-glycols provided the *trans*-isomers. Published by Elsevier Science Ltd.

1. Introduction

The Jocic reaction [the reaction of (trichloromethyl)carbinols with aqueous hydroxide to provide 2-substituted carboxylic acids] was first reported 100 years ago.[1] It has been revived and studied sporadically, particularly by Reeve et al.[2] and Benner et al.[3] More recently, Corey and Link described its application to the stereospecific syntheses of α-hydroxycarboxylic acids[4] and α-aminocarboxylic acids.[5] We employed a variation to synthesize 2-fluorocarboxylic acids which were subsequently converted to fluorinated analogs of several insect pheromones.[6] We then demonstrated that the 2-fluoroacids could be obtained in high enantiomeric purity under controlled reaction conditions.[7]

The reaction is usually portrayed as involving deprotonation of the (trichloromethyl)carbinol **1** followed by intramolecular displacement of chloride affording a reactive 1,1-dichloroepoxide **2** (Fig. 1). Nucleophilic opening (with inversion of configuration) of dichloroepoxide **2** gives the observed products. Thus an appropriately located internal nucleophile appeared to offer potential for ring formation; specifically, a vicinal OH ought to form an epoxide. Anticipating inversion at C-2, the relative configurations of the two OHs would determine the ultimate epoxide configuration.

* E-mail: joliver@asrr.arsusda.gov

0957-4166/98/$19.00 Published by Elsevier Science Ltd.
PII: S0957-4166(98)00156-6

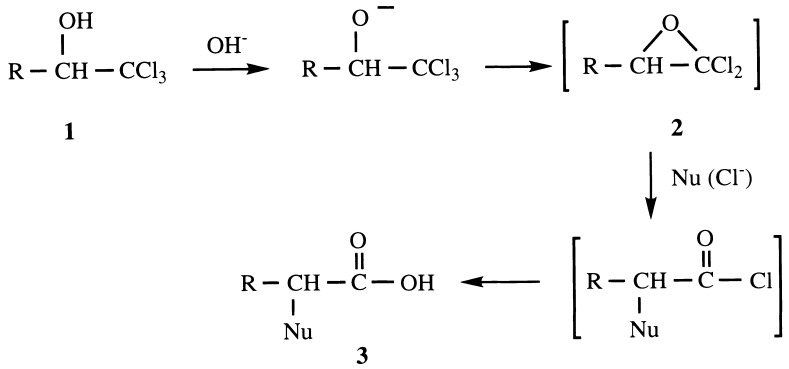

Fig. 1.

2. Results and discussion

The Corey group[8] described the conversion of aliphatic aldehydes to (trichloromethyl)carbinols of type **1** under essentially neutral conditions using sodium trichloroacetate and trichloroacetic acid in DMF. As a model chiral (trichloromethyl)glycol, we began with the readily available (*R*)-glyceraldehyde acetonide **4**. The carbinols **5** and **6** from **4** have been reported,[9] although formed electrolytically. Those authors assigned the (*R*,*R*)-configuration to the major isomer [ca. 2:1 over the (*R*,*S*)-isomer].[9,10] We applied the Corey procedure[8] to **4**[11] and obtained a mixture of **5** and **6** in a ratio of 63:37 (Fig. 2). The (*R*,*R*)-isomer **5** could be obtained directly by crystallization; flash chromatography of the mother liquor separated **6** from some additional **5**. [If the (*R*,*S*)-isomer is the desired product, the crude mixture of diols can be oxidized to the corresponding ketone; reduction of the latter with sodium borohydride gave **5** and **6** in a 1:3 ratio.]

Deprotection of the acetonides was achieved with trifluoroacetic acid in aqueous tetrahydrofuran.[12] To avoid possible complications from the distant OH and to improve solubility in organic solvents, the resulting triols **7** and **9** were not characterized but rather treated with 1 equiv. of t-butylchlorodimethylsilane to give the monosilyl derivatives **8** (*R*,*R*) and **10** (*R*,*S*). A methylene chloride solution of **8** was stirred (ice bath) with 5–6 equiv. of 40% tetrabutylammonium hydroxide for 1 h to provide, after workup and acid–base partitioning, a 65% yield of *trans*-epoxyacid **11** (2*R*,3*S*) as the only acidic product observed. The neutral fraction afforded t-butyldimethylsilanol in about 26% yield. Epoxyacid **11** was conveniently purified and characterized as its methyl ester **12**; the NMR spectra and specific rotation of **12** are in good agreement with those reported.[13]

The (*R*,*S*)-diol **10** was less reactive to tetrabutylammonium hydroxide than **8**, and a small amount of **10**, along with two neutral byproducts, could be detected after more than 2 h at room temperature (compared to the conversion of **8** that occurred smoothly at 0°C). After about 4.5 h, workup afforded the *cis*-epoxide **13** (2*R*,3*R*, 24% yield after flash chromatography of methyl ester **14**) as the only acidic product. Three neutral byproducts were observed: t-butyldimethylsilanol and two isomers of **10** (85:15 ratio) that evidently arose from silyl migration.

The structure of epoxyester **13** was supported by its ^{1}H- and ^{13}C-NMR spectra, and by comparison of its spectra to those published for the corresponding ethyl ester.[13]

All of the reactions described were also conducted with racemic materials (**4a** was prepared by TFAA/DMSO oxidation[14] of commercially available solketal); the racemic products and intermediates were used to establish that all were separable on chiral gas chromatographic columns, and as anticipated, all products from (*R*)-glyceraldehyde acetonide were single enantiomers at the stereogenic center emanating from the starting material. [Lack of stereospecificity in the intramolecular epoxide opening

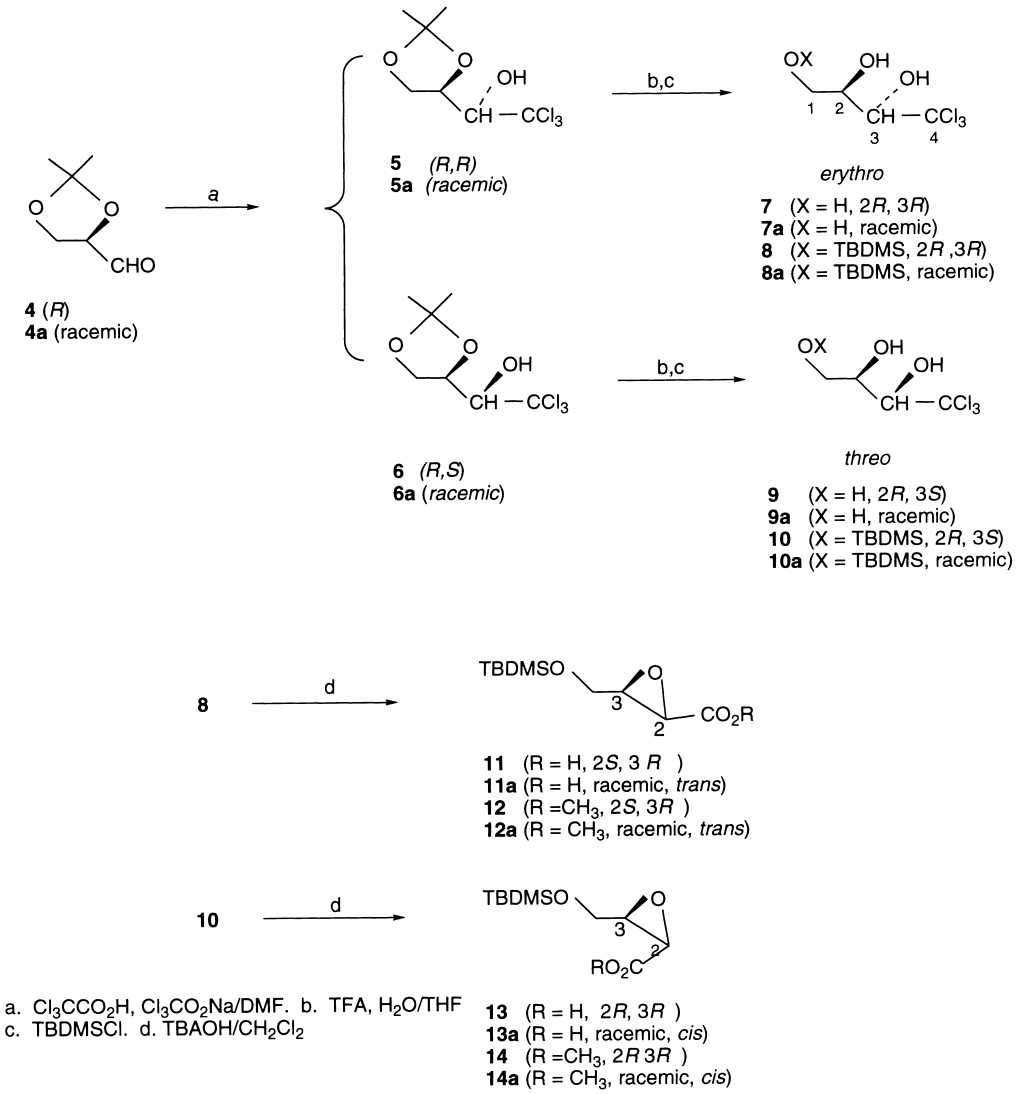

Fig. 2.

would, of course, have resulted in crossover to the wrong epoxide and not racemization; but in any event, so long as complete separation of **5** and **6** was achieved, no isomeric epoxides were observed in either case.]

Because of competing desilylation and silyl migration, future efforts will probably employ an alternative protecting group. Nonetheless, we have demonstrated stereospecific formation of chiral *cis*- and *trans*-epoxides from α-(trichloromethyl)glycols. The products contain two defined chiral centers and are four-carbon units with oxygen substitution at each carbon. They, or more appropriately protected analogs, may be useful synthons in carbohydrate or pheromone chemistry.

3. Experimental

^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker QE-300 spectrometer on deuteriochloroform

solutions. Mass spectra were obtained with a Finnigan Model 4510 GC–MS. Optical rotations were recorded from chloroform (used as received) solutions using a Perkin–Elmer Model 241 automatic polarimeter operated at the sodium-D (589 nm) wavelength. Chiral gas chromatography was performed on a Shimadzu Model 14A gas chromatograph fitted with a 30 m Chiraldex DBM column using hydrogen as the carrier gas. Combustion analyses were conducted by Galbraith Laboratories, Inc., Knoxville, TN. Mention of a proprietary company or product does not imply endorsement by the US Department of Agriculture.

*3.1. (*R,R*)-2,2-Dimethyl-α-(trichloromethyl)-1,3-dioxolane-4-methanol **5** and its (*R,S*)-isomer **6***

1,2:5,6-Di-O-isopropylidene-D-mannitol was cleaved with $NaIO_4$ according to a published procedure[11] and the crude product was extracted into dichloromethane and used without purification. In a representative case, 1.97 g of (*R*)-isopropylidene glyceraldehyde **4** in N,N-dimethylformamide (20 mL) was stirred in a water bath at room temperature, and trichloroacetic acid (3.5 g) was added followed by sodium trichloroacetate (3.5 g) in several portions.[8] After 1 h no remaining **4** could be detected by gas chromatography; the solution was diluted with ice–water and extracted with several portions of ether. The ether was diluted with about half its volume of pentane, then rinsed twice with water, dried over $MgSO_4$ and concentrated to give 2.67 g (70%) of a ca. 2:1 mixture of the previously reported[9,10] **5** and **6** as a tan solid. Typically, about two crystallizations from hexane at −10°C gave pure **5**: m.p. 82–83, $[\alpha]_D^{24}$=+24.5 (c 2.43, $CHCl_3$); ^{1}H-NMR: 1.38 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.11 (1H, d, J=4.5, OH), 4.09 (1H, dd, J=6.5 and 8.5, H-5a), 4.26 (1H, dd, J=6.5 and 8.5, H-5b), 4.35 (1H, dd, J=4.0 and 3.5, α-H), 4.58 (1H, J=3.5, 6.5 and 6.5, H-4); ^{13}C-NMR: 25.36 (CH_3), 26.36 (CH_3), 64.79 (C-5), 75.20, (C-4), 82.51 (α-C), 100.63 (CCl_3), 109.25 ($C(CH_3)_2$); MS (m/z, %) 237 (2.7), 235 (8.7), 233 (8.8), 177 (2.9), 175 (7.5), 173 (7.8). 101 (36.2), 73 (10.3), 72 (8.2), 61 (7.2), 59 (19.2), 43 (100). Combined mother liquors were concentrated and flash chromatographed on silica gel (toluene followed by 10 and 15% ethyl acetate in toluene) to provide **6**: $[\alpha]_D^{24}$=+12.1 (c 2.84, $CHCl_3$); ^{1}H-NMR: 1.43 (3H, s, CH_3), 1.48 (3H, s, CH_3), 3.88 (1H, d, J=8.5, OH), 4.06 (1H, dd, J=6.5 and 9.0, H-5a), 4.14 (1H, dd, J=8.5 and 2.5, α-H), 4.24 (1H, dd, J=6.5 and 9.0, H-5b), 4.56 (1H, dt, J=2.5, 6.5 and 6.5, H-4); ^{13}C-NMR: 25.70, 26.12, 68.47 (C-5), 73.35 (C-4), 81.27 (α-C), 101.36 (CCl_3), 110.91 ($C(CH_3)_2$); MS (m/z, %) 237 (4.5), 235 (13.3), 233 (13.7), 157 (2.1), 144 (10.7), 153 (15.6), 111 (6.3), 109 (10.1), 61 (9.5), 59 (55.0), 43 (100) followed by some additional **5**. As indicated in the text, the isomeric ratio could be skewed to favor **6** by oxidation and reduction with $NaBH_4$; however oxidation of the mixture of **5** and **6** with pyridinium chlorochromate was very sluggish, requiring about a week in refluxing dichloromethane to go to completion. Other oxidants have not been investigated.

*3.2. Deacetalization and conversion to mono t-butyldimethylsilyl ethers **8** and **10***

A solution of the (*R,S*)-carbinol **6** (390 mg, 1.56 mmol) in tetrahydrofuran (4 mL) and water (2 mL) was treated with trifluoroacetic acid (100 μL)[12] and the solution was heated at 60–70°C for 3 h, then allowed to stand overnight at room temperature. The solvent was evaporated and a small portion of toluene was added and evaporated to remove any residual water. N,N-Dimethylformamide (2.5 mL), imidazole (142 mg) and t-butyldimethylchlorosilane (284 mg, 1.88 mmol) were added. After 4.5 h at room temperature, the mixture was partitioned between ether:hexane (1:1, v:v) and aqueous sodium bicarbonate. The organic phase was rinsed with water, dried, and concentrated to provide 540 mg of a clear oil that was flash chromatographed on silica gel (10–20% ethyl acetate in hexanes) to provide pure monoTBDMS **10** as a colorless oil (93%): $[\alpha]_D^{24}$=−4.89 (c 2.70, $CHCl_3$); ^{1}H-NMR: 0.10 (6H, s), 0.90

(9H, s), 2.73 (1H, br s, OH), 3.67 (2H, d J=6.5, H-1), 3.99 (1H, br s, H-3a), 4.31 (1H, t, J=6.5, H-2); ^{13}C-NMR: −5.38, 18.27 ($C(CH_3)_3$), 25.83, (CH_3), 64.74 (CH_2), 68.83, 80.09 (CHOH), 102.33 (CCl_3); MS (m/z, %), 219 (4.6), 217 (4.1), 155 (7.3), 153 (19.1), 119 (17.1), 117 (89.4), 103 (14.5), 101 (9.6), 95 (12.3). 93 (29.7), 91 (12.4), 89 (45.7), 77 (16.6), 76 (10.9), 75 (100), 74 (8.8), 73 (74.8), 61 (11.9), 59 (31.0), 58 (12.8), 57 (12.9), 47 (14.5), 45 (19.8), 43 (23.1), 41 (17.1).

The same procedure applied to the (*R*,*R*)-isomer **5** provided monoTBDMS ether **8** (64% after flash chromatography): $[\alpha]_D^{24}$=+1.37 (c 3.80, $CHCl_3$); ^{1}H-NMR: 0.11 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 2.83 (1H, d, J=7.5, H-3), 3.91 (1H, dd J=6.5 and 13.9), 4.10 (1H, dt, J=3.4 and 8.1, H-1a), 4.28 (1H, dd, J=6.5 and 14.0); ^{13}C-NMR: −5.50, 18.20 ($C(CH_3)_3$), 25.83 (CH_3), 64.69 (CH_2), 70.24, 85.38 (CHOH), 105.25 (CCl_3); MS (m/z, %), 185 (7.8), 183 (11.8), 155 (9.2), 153 (24.2), 119 (8.4), 117 (76.3), 103 (12.5), 101 (7.6), 95 (7.9). 93 (20.6), 91 (13.0), 89 (36.6), 77 (11.8), 76 (4.5), 75 (100), 74 (6.2), 73 (52.9), 61 (6.8), 59 (19.6), 58 (8.3), 57 (9.2), 47 (10.0), 45 (13.6), 43 (12.5), 41 (12.1).

*3.3. Conversion of mono t-butyldimethylsilyl ether **10** to the TBDMS ether of (2*R*,3*R*)-methyl 3-(hydroxymethyl)oxiranecarboxylate **14***

A solution of **10** (325 mg, ~1 mmol) in dichloromethane (2.5 mL) was added slowly to a cold (ice bath) stirred mixture of dichloromethane (9 mL) and 40% aqueous tetrabutylammonium hydroxide (4.5 mL). The ice bath was removed and the mixture was stirred at room temperature for 4.5 h, then most of the dichloromethane was removed on a rotary evaporator at room temperature and the residue was partitioned between water and ether. The ether solution was rinsed with water and brine, then was dried and concentrated to give 38 mg of a colorless oil that contained some t-butyldimethylsilanol and two apparent isomers of **10**. The combined aqueous phases were neutralized with a slight excess of 2 N $KHSO_4$ and extracted with several portions of ether. The combined ether extracts were rinsed successively with 2 N $KHSO_4$, water and brine, then were dried, concentrated, and treated with ethereal diazomethane until the yellow color persisted. The excess diazomethane was removed with a stream of nitrogen in a hood, then the remaining solvent was removed with a rotary evaporator. Flash chromatography (5, 10, 20% ethyl acetate in hexanes) provided the *trans*-(*R*,*R*)-epoxyester **14** (59 mg, 24%) as a colorless oil: $[\alpha]_D^{24}$=−20.3 (c 3.81, $CHCl_3$); ^{1}H-NMR: 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 3.31 (1H, dd, J=4.5 and 5.5, H-3), 3.44 (1H, d, J=4.5, H-2), 3.76 (1H, dd, J=5.5 and 11.5, H-4a), 3.73 (3H, s, CH_3), 3.90 (1H, dd, J=5.5 and 11.5); ^{13}C-NMR: −5.40, (CH_3Si), 18.36 ($C(CH_3)_3$), 25.83 ($C(CH_3)_3$), 50.16 (C-3), 52.35 (OCH_3), 58.20 (C-2), 61.40 (O–CH_2), 168.71 (C=O); MS (m/z, %) 215 (3.8), 161 (10.2), 159 (48.3), 157 (13.8), 131 (15.2), 129 (47.1), 115 (10.2), 101 (45.3), 91 (5.6), 90 (9.0), 89 (100), 83 (38.4), 75 (78.3), 73 (38.1), 61 (10.6), 59 (60.3), 57 (10.0), 55 (11.7), 45 (19.1), 41 (15.3). Anal. calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.96; H, 9.17.

*3.4. Conversion of mono t-butyldimethylsilyl ether **8** to the TBDMS ether of (2*S*,3*R*)-methyl 3-(hydroxymethyl)oxiranecarboxylate **12***

This was performed similarly except that this reaction was complete in 1 h at ice bath temperature. Similar workup gave 35 mg of neutral product that was essentially all t-butyldimethylsilanol. The acidic fraction, after esterification with diazomethane and flash chromatography, yielded 109 mg (47%) of pure **12**: $[\alpha]_D^{24}$=+26.0 (c 2.01, $CHCl_3$); ^{1}H-NMR: 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 3.34 (1H, dd, J=1.8 and 5.0, H-3), 3.54 (1H, d, J=1.8, H-2), 3.76 (1H, dd, J=2.5 and 12.0), 3.77 (3H, s), 3.90 (1H, dd, J=2.5 and 12.0, OCH_2); ^{13}C-NMR: −5.43 and −5.30 (CH_3Si), 18.38 ($C(CH_3)_3$), 25.81 ($C(CH_3)_3$), 51.81 (C-3), 52.26 (OCH_3), 57.42 (C-2), 60.55 (O–CH_2), 168.18 (C=O); MS (m/z, %) 161 (9.9), 159 (37.6), 157

(11.3), 131 (8.4), 129 (29.3), 114 (8.0), 101 (39.9), 91 (5.3), 90 (8.4), 89 (100), 83 (36.0), 75 (75.8), 73 (30.7), 61 (9.8), 59 (55.3), 58 (7.6), 57 (9.5), 55 (10.5), 47 (7.0), 45 (10.0), 41 (13.4). Anal. calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.81; H, 9.25.

Acknowledgements

We are grateful to Ms. Sini Panicker for skilled technical assistance and to Mr. Dave DeVilbiss for mass spectra.

References

1. Jocic, Z. *Zh. Russ. Fiz. Khim. Ova*. **1897**, *29*, 97.
2. Reeve, W.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem*. **1980**, *58*, 485–493 and references therein.
3. Benner, J. P.; Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 311–342.
4. Corey, E. J.; Link, J. O. *Tetrahedron Lett*. **1992**, *33*, 3431–3434.
5. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc*. **1992**, *114*, 1906–1909.
6. Oliver, J. E.; Waters, R. M.; Lusby, W. R. *Synthesis* **1994**, 273–274.
7. Khrimian, A. P.; Oliver, J. E.; Waters, R. M.; Panicker, S.; Nicholson, J. M.; Klun, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 37–40.
8. Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett*. **1992**, *33*, 3435–3438.
9. Shono, T.; Ohmizu, H.; Kise, N. *Tetrahedron Lett*. **1982**, *23*, 4801–4804.
10. Shono, T.; Kise, N.; Suzumoto, T. *J. Am. Chem. Soc*. **1984**, *106*, 259–260.
11. Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403–406.
12. Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc*. **1981**, *103*, 5813–5821.
13. Saito, S.; Nagao, Y.; Miyazaki, M.; Inaba, M.; Moriwake, T. *Tetrahedron Lett*. **1986**, *27*, 5249–5252.
14. Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem*. **1987**, *52*, 4851–4855.