Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 311–314
Tetrahedron Letters

Synthesis of novel amino squaric acids via addition of dianion enolates derived from *N*-Boc amino acid esters

Toshikazu Ishida, Tetsuro Shinada* and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558-8585, Japan

Received 30 September 2004; revised 1 November 2004; accepted 5 November 2004

Abstract—Novel α-amino squaric acid analogs were synthesized by initial addition reaction of a dianion enolate generated from *N*-Boc amino acid *tert*-butyl ester to squaric acid diisopropyl ester, and subsequent decarboxylation of the resulting carboxylic acid moiety.

The carboxyl group in α-amino acids is an important functional group as a proton-donating or an amide bond-forming group.[1] It has been recognized that sulfonic acid,[2] phosphonic acid,[3] boronic acid,[4] and tetrazole[5] can serve as an important surrogate for the carboxyl group of α-amino acids (Fig. 1). Many synthetic studies and applications of these analogs focusing on their metabolic stability, inhibitory effects to proteases,[6] and potency for catalytic antibodies[7] have been reported.

Sulfonic acid **3** and phosphonic acid **4** are tetrahedral surrogates. Boric acids **5** and tetrazoles **6** are planar analogs while they are weak acids and are unable to be employed for peptide coupling reactions. Phosphonate analogs can be used for peptide coupling reaction via selective protection and activation of the two hydroxy groups. In this context, development of an amino acid analog that possesses a planar conjugate system and acidic functionality serving for peptide coupling reactions is a challenging task in this area. In this paper, we report the synthesis of novel amino acid analog **2** bearing a 2-hydroxy-3,4-dioxocyclobut-1-enyl (sq) group known as a planar square acid surrogate via a carbon–carbon bonds.[8] Squaric acid belongs to a class of oxocarbons and exhibits unique physicochemical properties, for example, strong acidity, aromaticity, strained ring, electron deficiency, and metal chelating ability.[9] The sq group has received considerable attention as a carboxylic acid mimic in medicinal chemistry,[10] a novel chromophore in material science,[11] a new chelator in inorganic chemistry,[12] and a starting material for a synthon of quinones, triquinanes, cyclopentenones, and furanones in organic synthesis.[13] Recently, squaric

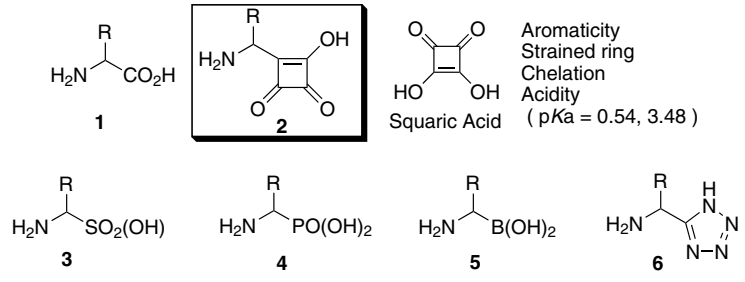
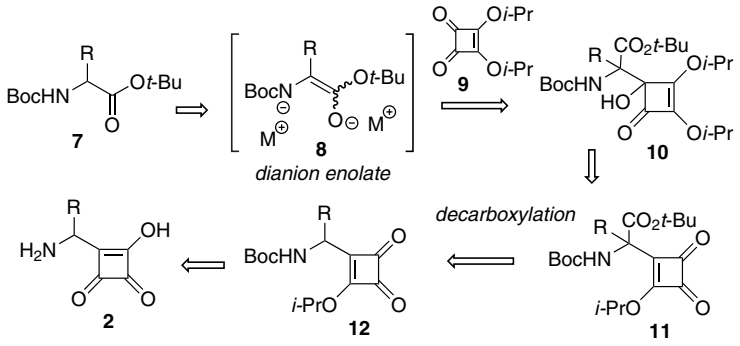


Figure 1.

Keywords: Amino acid; Squaric acid; Dianion enolate.
* Corresponding authors. Tel.: +81 6 6605 3193; fax: +81 6 6605 3153; e-mail addresses: shinada@sci.osaka-cu.ac.jp; ohfune@sci.osaka-cu.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.044

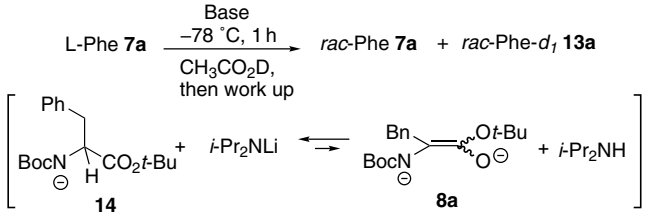


Scheme 1.

acid diesters are employed for a linker to develop bioconjugate molecules by means of a facile substitution of a squaric acid diester with amines.[14] These multifunctional characteristics prompted us to develop novel sq-amino acid analog **2**.

We planned a simple access to **2** from readily available *N*-Boc α-amino acid esters such as Phe, Ala, etc. (Scheme 1). To this end, an addition of dianion enolate **8**[15] derived from *N*-Boc α-amino acid esters **7** to squaric acid diester **9** followed by decarboxylation reaction (**11** to **12**) was devised according to our previous synthesis of sq-Gly (**2**: R = H) from a dianion enolate **8**.[16] Initially, we examined an addition reaction of **9** to a dianion enolate **8a** (R = Bn). Treatment of Boc-L-Phe *tert*-butyl ester **7a** with 2.2 equiv of LDA in THF at −78 °C followed by addition of **9** gave the desired adduct **10a** in low yield (Scheme 2).

The above insufficient results led us to examine the magnitude of the enolization by means of deuterium incorporation experiments (Scheme 3, Table 1). Treatment of L-**7a** with 2.2 equiv of LDA at −78 °C followed by quenching with CH_3CO_2D afforded a mixture of *d*-atom incorporated **13a** and undeuterated **7a** in 89% yield (**13a**:**7a** = 33:67, entry 1). Even the use of 6 equiv of LDA gave 51% incorporation ratio (entry 2), suggesting that the enolizations by LDA were insufficient.[17] However, we found that the optical rotation of a mixture of **13a** and **7a** was extremely reduced indicating that the starting L-**7a** was racemized via the enolate **8a** by using LDA. A proposed reaction pathway to explain these results is depicted in Scheme 3. Dianion enolate **8a** would be basic enough to deprotonate the resulting *i*-Pr_2NH. Therefore, a proton exchanging equilibrium would exist in situ prior to quenching with CH_3CO_2D. Protonation of **14** and **8a** afforded *rac*-Phe **7a** and **13a**, respectively. The deprotonation efficiency was assessed



Scheme 3.

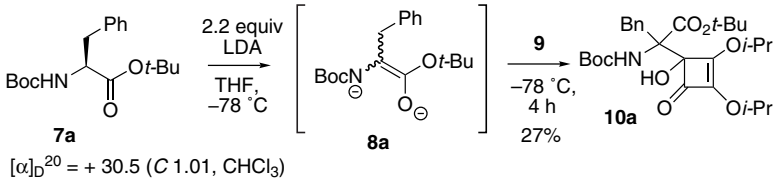
Table 1. Deprotonation experiments of **7a**

Entry	Base[a] (pK_a)[b]	*d*-Incorporation[d] (%)	$[\alpha]_D$[e] and Racemization ratio[f] (%)
1	LDA (35.7)	33	+7.36:76
2	LDA[c]	51	+1.58:95
3	LHMDS (29.5)	<1	+30.2:<1
4	LTMP (37.3)	43	+5.96:81

[a] Conditions: 2.2 equiv base, THF, −78 °C, 1 h.
[b] Ref. 18.
[c] 6 equiv of LDA was used.
[d] Determined by ^{1}H NMR.
[e] Values of a mixture of **7a** and **13a**.
[f] Based on the $[\alpha]_D$ value.

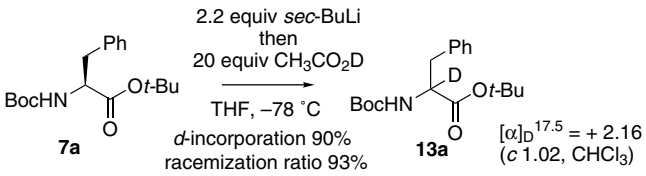
with lithium 1,1,1,3,3,3-hexamethyldisilazide (LHMDS) or lithium 2,2,6,6-tetramethylpiperidide (LTMP). LHMDS was not effective at all due probably to its lower basicity in comparison with that of LDA (entry 3).[18] The use of more basic and bulky LTMP gave slightly better *d*-incorporation ratio (43%) accompanied by a large loss of the optical rotation (entry 4).[19]

On the basis of the above results, we anticipated that the use of *sec*-BuLi instead of amine bases would be advantageous for the exclusive formation of the dienolate **8a**



$[\alpha]_D^{20}$ = + 30.5 (*C* 1.01, $CHCl_3$)

Scheme 2.



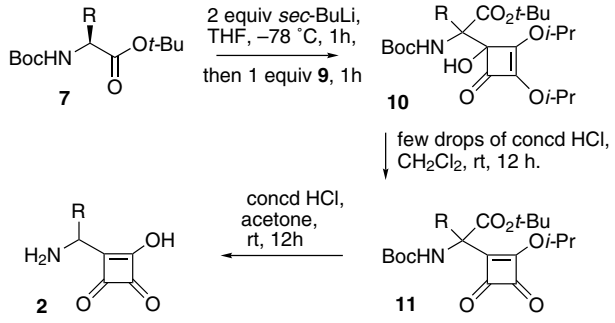
Scheme 4.

(Scheme 4). As expected, the magnitude of *d*-incorporation ratio (90%) and loss of the optical rotation (93%) were found to be nearly equal when 2.2 equiv of *sec*-BuLi was used. Thus, an effective method for generation of a dianion enolate from easily available Boc-protected amino acid esters using *sec*-BuLi was established.

With efficient method for the dianion enolate formation in hand, we next examined its condensation with **9**. Treatment of **7a** with *sec*-BuLi in THF at −78 °C followed by addition of **9** gave the desired adduct **10a** in 69% yield. Thus, it was found that the improved ratio of the enolate formation directly reflected to an increase in the product yield. The dianion enolate derived from various amino acid *tert*-butyl esters **7b–h** reacted smoothly with **9** to give the corresponding adducts **10b–h** in satisfactory yields (Table 2).

Conversion of **10a–h** to the sq-amino acids **2a–h** were performed according to our previous method.[16] Thus, the adduct **10a** was treated with a small amount of concd HCl in CH_2Cl_2 to give cyclobutenedione **11a**. Exposure to concd HCl in acetone occurred simultaneous decarboxylation and removal of the protecting groups to give sq-Phe **2a**. Thus sq-Phe **2a** was prepared from **7a** in three steps. The overall yield was 39%. Other adducts **10b–h** were converted in a similar manner as those of **2a** to the corresponding sq-amino acids **2b–h**[20] in good to moderate yields (Table 2).

Table 2. Synthesis of sq-amino acids **2a–h**



Series	Yields[a] (%) **10a–h**	Yields[b] (%) **11a–h**	Yields[c] (%) **2a–h**
a: Phe	69	78	72
b: Tyr	50[d]	77	74
c: Ala	75	75	65
d: Leu	52	79	46
e: Ile	43	85	50
f: Allylgly	70	75	80
g: Val	36	70	70
h: Pro	53	81	36

[a] Yields from **7a**,**b**.
[b] Yields from **10a**,**b**.
[c] Yields from **11a**,**b**.
[d] 3.3 equiv of *sec*-BuLi was used.

In summary, we have developed a concise synthetic route to access sq-amino acids by addition of dianion enolates derived from easily available *N*-Boc α-amino acid esters to squaric acid diester followed by the decarboxylation reaction. The key to the synthesis was effective generation of the dianion enolate based on the elucidation of their equilibrium behavior. Further studies with respect to incorporation of the novel sq-amino acids into bioactive peptides are in progress.

Acknowledgements

This study was supported by a grant from the Research for the Future Program (99L01204) and Grant-in-Aid (No. 15510178) from the Japan Society for the Promotion of Science (JSPS).

References and notes

1. Greenstein, J. P.; Winitz, M. In *Chemistry of the Amino Acids*; John Wiley and Sons: New York, 1961; Vol. 1–3.
2. Bajusz, Z.; Ronai, A. Z.; Szekely, J. I.; Turan, A.; Juhasz, A.; Patthy, A.; Miglecz, E.; Berzetei, I. *FEBS Lett.* **1980**, *117*, 308–310.
3. (a) Kafarski, P.; Lejczak, B. In *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley and Sons, 2000; For recent examples see: (b) Kobayahi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558–6559; (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; (d) Azizi, N.; Saidi, M. *Tetrahedron* **2003**, *59*, 5329–5332; (e) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Lopez de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689–700.
4. For a review, see: Dembitsky, V. M.; Srebnik, M. *Tetrahedron* **2003**, *59*, 579–593.
5. (a) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525–2527; For reviews, see: (b) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379–3393; (c) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.
6. (a) Wallace, E. M.; Moliterni, J. A.; Moskal, M. A.; Neubert, A. D.; Marcopulos, N.; Stamford, L. B.; Trapani, A. J.; Savage, P.; Chou, M.; Jeng, A. Y. *J. Med. Chem.* **1998**, *41*, 1513–1523; (b) Du, S.; Tsipori, H.; Baasov, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2469–2472; (c) Bartlett, P. A.; Acher, F. *Bull. Chim. Soc., Fr.* **1986**, 771–775.
7. (a) Gouverneur, V.; Lalloz, M.-N. *Tetrahedron Lett.* **1996**, *37*, 6331–6334; (b) Hischmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237; (c) Schultz, P. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *10*, 1283; (d) Shultz, P. G. *Acc. Chem. Res.* **1989**, *22*, 287.
8. Squaric acid as amino acid isosteres, see: Kinney, W. A.; Abou-Gharbia, M.; Garrison, D. T.; Schmid, J.; Kowal, D. M.; Bramlett, D. R.; Miller, T. L.; Tasse, R. P.; Zaleska, M. M.; Moyer, J. A. *J. Med. Chem.* **1998**, *41*, 236–246.

9. For reviews, see: (a) Seitz, G.; Imming, P. *Chem. Rev.* **1992**, *92*, 1227–1260; (b) West, R.; Niu, J. In *Nonbenzenoid Aromatics*; Snyder, J. P., Ed.; Academic: New York, 1969; pp 311–346; (c) Schmidt, A. H. *Synthesis* **1980**, 961–994.
10. For recent examples see: (a) Shinada, T.; Nakagawa, Y.; Hayashi, K.; Corzo, G.; Nakajima, T.; Ohfune, Y. *Amino Acids* **2003**, *24*, 293–302; (b) Childers, W. E., Jr.; Abou-Gharbia, M. A.; Moyer, J. A.; Zaleska, M. M. *Drugs Future* **2002**, *27*, 633–638; (c) Sato, K.; Seio, K.; Sekine, M. *J. Am. Chem. Soc.* **2002**, *124*, 12715–127124.
11. For recent examples, see: (a) Block, M. A. B.; Khan, A.; Hecht, S. *J. Org. Chem.* **2004**, *69*, 184–187; (b) Bueschel, M.; Ajayaghosh, A.; Arunkumar, E.; Daub, J. *Org. Lett.* **2003**, *5*, 2975–2978; (c) Pham, W.; Weissleder, R.; Tung, C.-H. *Tetrahedron Lett.* **2003**, *44*, 3975–3978; (d) Jiao, G.-S.; Loudet, A.; Lee, H. B.; Kalinin, S.; Johansson, L.B.-A.; Burgess, K. *Tetrahedron* **2003**, *59*, 3109–3116.
12. For recent examples, see: (a) Carranza, J.; Brennan, C.; Sletten, J.; Vangdal, B.; Rillema, P.; Lloret, F.; Julve, M. *New J. Chem.* **2003**, *27*, 1775–1783; (b) Modec, B.; Brencic, J. V.; Burkholder, E. M.; Zubieta, J. *Dalton Trans.* **2003**, 4618–4625; (c) Dolbecq, A.; Mialane, P.; Lisnard, L.; Marrot, J.; Secheresse, F. *Chem. Eur. J.* **2003**, *9*, 2914–2920; (d) Yang, C.-H.; Chuo, C.-M.; Lee, G.-H.; Wang, C.-C. *Inorg. Chem. Commun.* **2003**, *6*, 135–140; (e) For reviews, see:Hall, L. A.; Williams, D. J. *Adv. Inorg. Chem.* **2001**, *52*, 249–291; (f) Aime, S.; Botta, M.; Fasano, M.; Geninatti Crich, S.; Terreno, E. *Coord. Chem. Rev.* **1999**, *185–186*, 321–333.
13. For recent examples, see: (a) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155–13164; (b) Buchynskyy, A.; Kempin, U.; Vogel, S.; Hennig, L.; Findeisen, M.; Muller, D.; Giesa, S.; Knoll, H.; Welzel, P. *Eur. J. Org. Chem.* **2002**, *7*, 1149–1162; (c) Pena-Cabrera, E.; Liebeskind, L. S. *J. Org. Chem.* **2002**, *67*, 1689–1691; For reviews, see: (d) Clausen, C.; Wartchow, R.; Butenschon, H. *Eur. J. Org. Chem.* **2001**, 93–113; (e) Liu, H.; Tomooka, C. S.; Xu, S. L.; Yerxa, B. R.; Sullivan, R. W.; Xiong, Y.; Moore, H. W. *Org. Synth.* **1999**, *76*, 189–198; (f) Ohno, M.; Yamamoto, Y.; Eguchi, S. *Synlett* **1998**, 1167–1174; (g) Moore, H. W.; Yerxa, B. R. *Chemtracts: Org. Chem.* **1992**, *5*, 273–313.
14. For recent examples, see: (a) Saksena, R.; Chernyak, A.; Poirot, E.; Kovac, P. *Methods Enzymol.* **2003**, *362*, 140–159; (b) Porter, J. R.; Archibald, S. C.; Childs, K.; Critchley, D.; Head, J. C.; Linsley, J. M.; Parton, T. A. H.; Robinson, M. K.; Shock, A.; Taylor, R. J.; Warrellow, G. J.; Alexander, R. P.; Langham, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1051–1054; (c) Bergh, A.; Magnusson, B.-G; Ohlsson, J.; Wellmar, U.; Nilsson, U. J. *Glycoconjugate J.* **2001**, *18*, 615–621.
15. (a) Generation of dianion enolates from *N*-Boc amino acid esters and their synthetic utilities have not been well examined. Chemistry of dianion enolates from *N*-acyl amino acid esters, see: Kazmaier, U.; Pahler, S.; Endermann, R.; Habich, D.; Kroll, H.-P.; Riedl, B. *Bioorg. Med. Chem.* **2002**, *10*, 3905–3913; (b) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602–4607; (c) Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329; (d) Dikshit, D. K.; Singh, S. *Tetrahedron Lett.* **1988**, *29*, 3109–3110; (e) Evans, D. A.; Sidebottom, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 753–754.
16. Shinada, T.; Hayashi, K.; Hayashi, T.; Yoshida, Y.; Horikawa, M.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Org. Lett.* **1999**, *1*, 1663–1666. An alternative approach for sq-Gly, see: Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470–1472.
17. Similar examples in monoanion enolates, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654; (b) Shimamoto, K.; Ohfune, Y. *Synlett* **1993**, 919–920.
18. Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3443–3444.
19. Similar results were observed in the deprotonation experiments of sterically less hindered Boc-L-Phe methyl ester. (LDA: *d*-incorporation 33%, racemization ratio 86%; LTMP: *d*-incorporation 44%, racemization ratio 89%). These facts indicated that the equilibrium was not influenced by the steric demand.
20. Melting points (dec, recrystallized from H_2O–MeOH) and ^1H NMR data of **2a**–**h** in DMSO-d_6 **2a**: 220–221 °C; ^1H NMR (300 MHz) δ 8.39 (br s, 3H), 7.27 (m, 5H), 4.25 (br s, 1H), 3.26 (dd, J = 13.0, 4.8 Hz, 1H), 3.13 (dd, J = 13.0, 4.8 Hz, 1H); **2b**: 230–231 °C; ^1H NMR (400 MHz) δ 9.27 (br s, 1H), 8.14 (br s, 3H), 6.99 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 4.18 (br s, 1H), 3.13 (dd, J = 13.4, 8.8 Hz, 1H), 2.94 (dd, J = 13.4, 5.6 Hz, 1H); **2c**: 231–232 °C; ^1H NMR (300 MHz) δ 8.21 (br s, 3H), 4.21 (br s, 1H), 1.40 (d, J = 6.6 Hz, 3H); **2d**: 213–214 °C; ^1H NMR (300 MHz) δ 8.07 (br s, 3H), 4.06 (dd, J = 9.5, 5.7 Hz, 1H), 1.89–1.49 (m, 3H), 0.86 (d, J = 6.0 Hz, 6H); **2e**:[21] 200–201 °C; ^1H NMR (400 MHz) δ 8.79 (br s, 3H), 4.57 (m, 5/8H), 4.49 (m, 3/8H), 2.08 (m, 3/8H), 1.95 (m, 5/8H), 1.83–1.54 (m, 2H), 1.48 (d, J = 6.8 Hz, 9/8H), 1.47–1.41 (m, 30/8H), 1.38 (t, J = 7.3 Hz, 9/8H); **2f**: 198–199 °C; ^1H NMR (300 MHz) δ 8.05 (br s, 3H), 5.67 (ddt, J = 17.2, 10.1, 7.0 Hz, 1H), 5.06 (d, J = 17.0 Hz, 1H), 5.00 (d, J = 10.1 Hz, 1H), 4.07 (br t, J = 6.0 Hz, 1H), 2.66–2.38 (m, 2H); **2g**: 199–200 °C; ^1H NMR (400 MHz) δ 8.12 (br s, 3H), 3.89 (m, 1H), 2,14 (octet, J = 6.8 Hz, 1H), 0.93 (d, J = 6.84 Hz, 3H), 0.89 (d, J = 6.84 Hz, 3H); **2h**: 219–220 °C; ^1H NMR (400 MHz) δ 9.27 (br s, 1H), 8.67 (br s, 1H), 4.44 (br s, 1H), 3.3–3.1 (m, 2H), 1.85–2.20 (m, 4 H).
21. The compound **2e** (4-((1*R*,2*S*)- and (1*S*,2*S*)-1-amino-2-methylbutyl)-3-hydroxycyclobut-3-ene-1,2-dione, [sq-isoleucine])was obtained as an inseparable 5:3 mixture of diastereomers at the carbon attached to the amino group. The absolute stereochemistry at C-1 and C-2 are *R*/*S* (5:3 or 3:5) and *S*, respectively. The integral values of the protons were indicated as a number of observed H/8.