

(S)-Pramipexole and Its Enantiomer, Dexpramipexole: A New Chemoenzymatic Synthesis and Crystallographic Investigation of Key Enantiomeric Intermediates

Samuele Ciceri ^{1*}, Patrizia Ferraboschi ¹, Paride Grisenti ², Shahrzad Reza Elahi ¹, Carlo Castellano ³, Matteo Mori ⁴ and Fiorella Meneghetti ^{4*}

¹ Department of Medical Biotechnology and Translational Medicine, University of Milan, Via C. Saldini 50, 20133 Milano, Italy; shahrzad.rezaelahi@gmail.com (S.R.); patrizia.ferraboschi@unimi.it (P.F.)

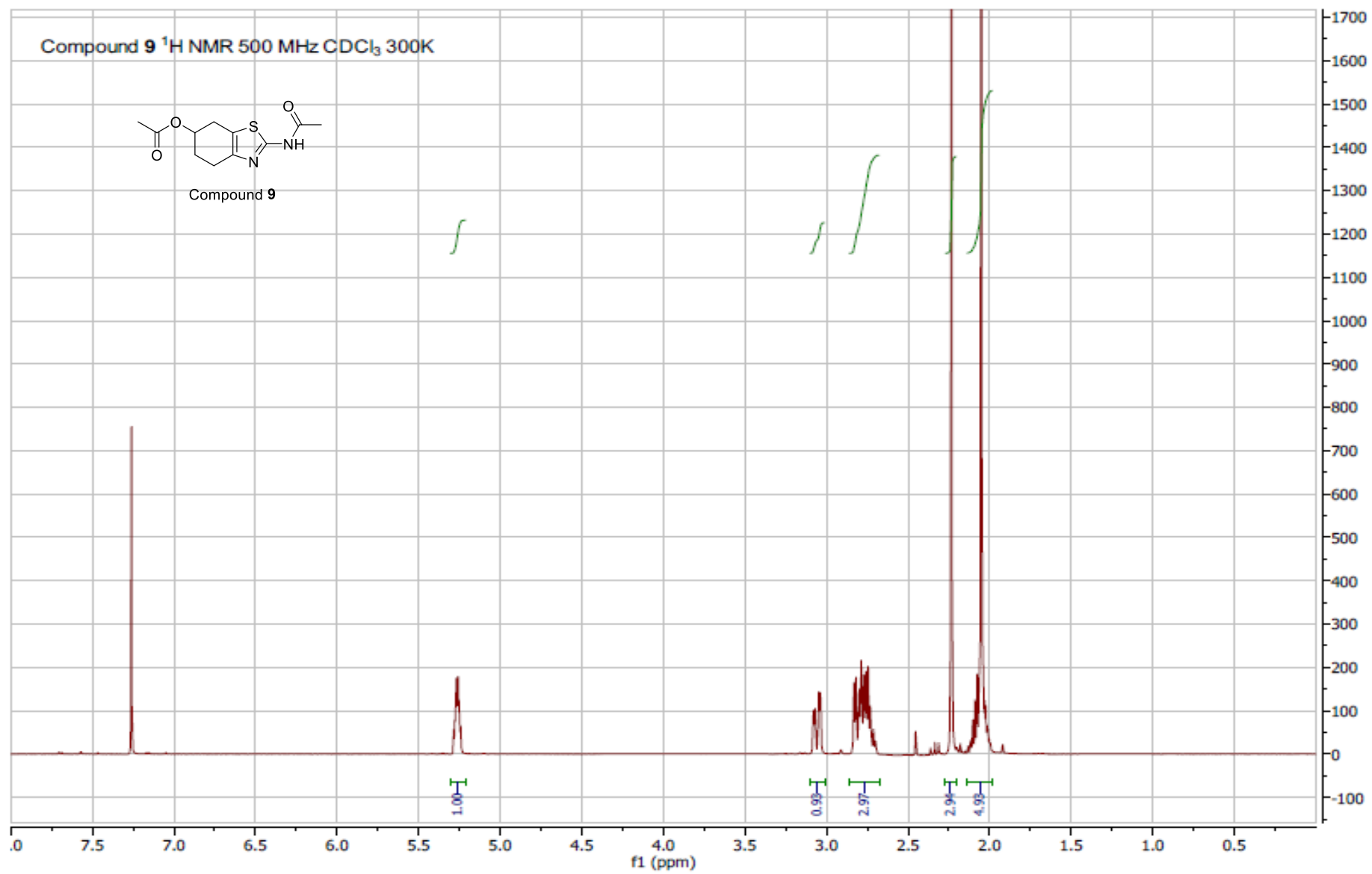
² Chemical-Pharmaceutical Consulting and IP Management, Viale G. da Cermenate 58, 20141 Milano, Italy; grisenti.paride60@gmail.com (P.G.)

³ Department of Chemistry, University of Milan, Via C. Golgi 19, 20133, Milan, Italy; carlo.castellano@unimi.it (C.C.)

⁴ Department of Pharmaceutical Sciences, University of Milan, Via L. Mangiagalli 25, 20133 Milano, Italy; matteo.mori@unimi.it (M.M.)

* Correspondence: samuele.ciceri@guest.unimi.it; Tel: +39 0250316052 (S.C.); fiorella.meneghetti@unimi.it; Tel: +39 0250319306 (F.M.)

SUPPLEMENTARY MATERIALS



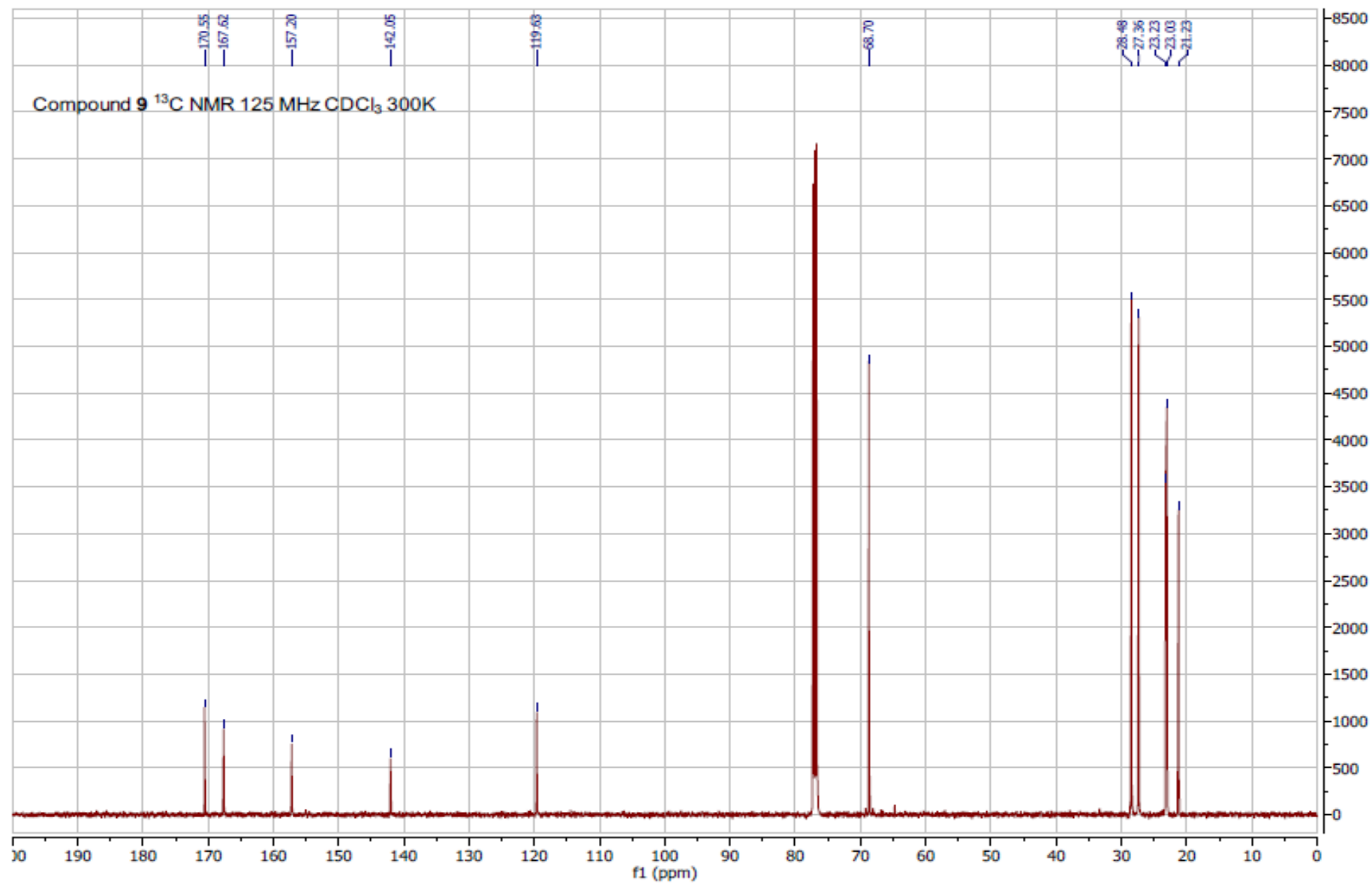


Figure S2. ^{13}C NMR of compound **9**

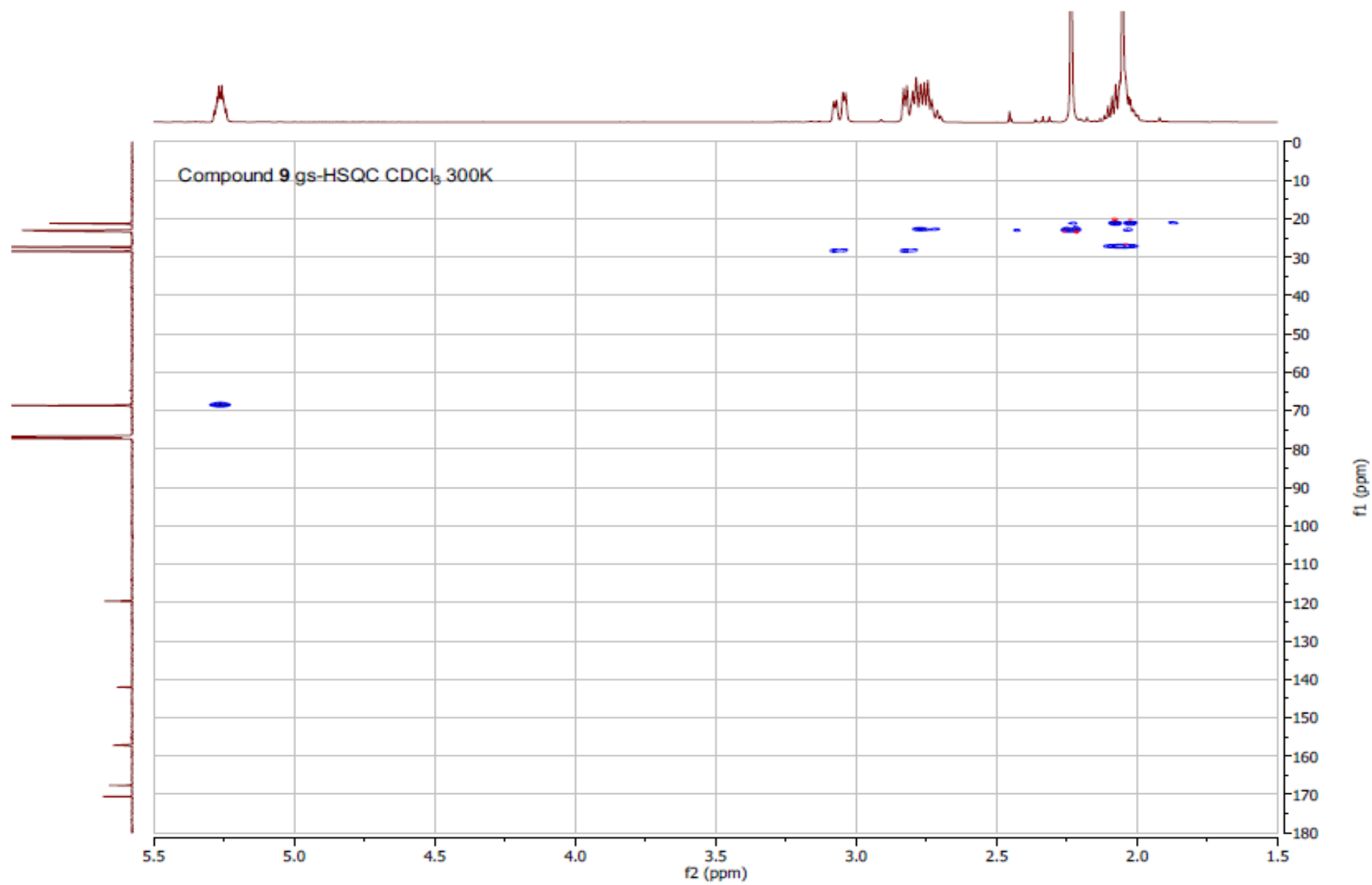


Figure S4. HSQC of compound **9**

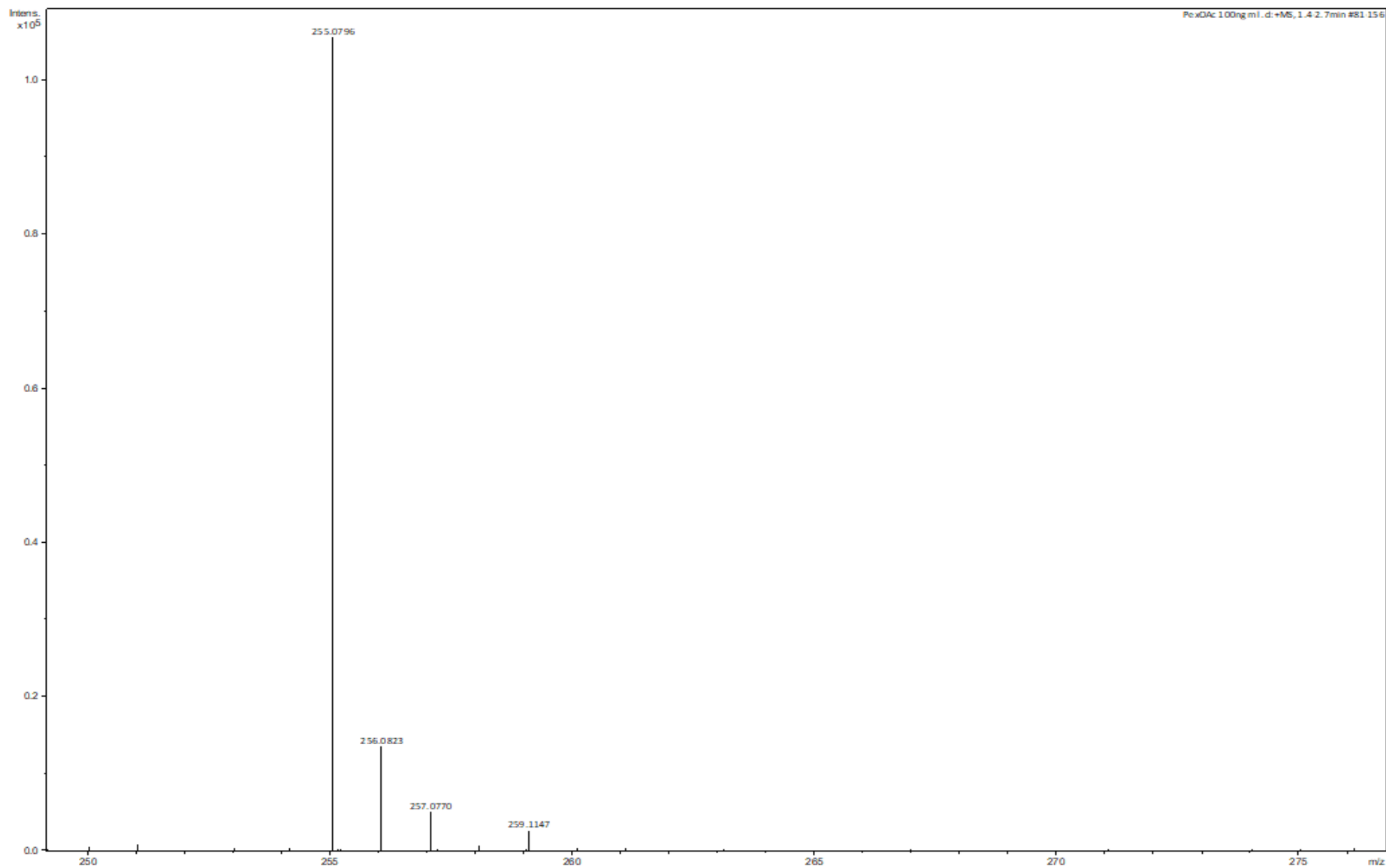


Figure S5. HRMS of compound **9**

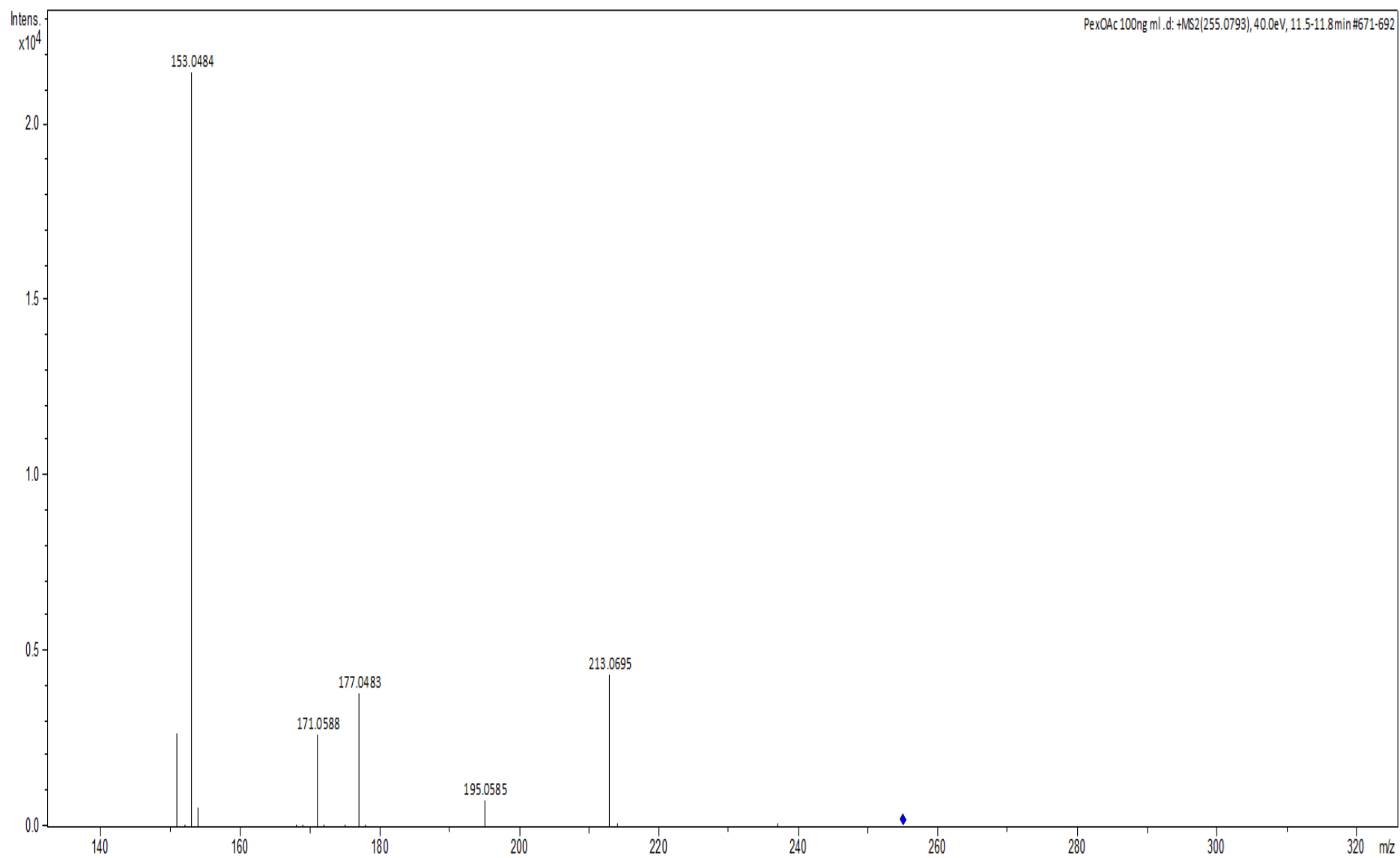
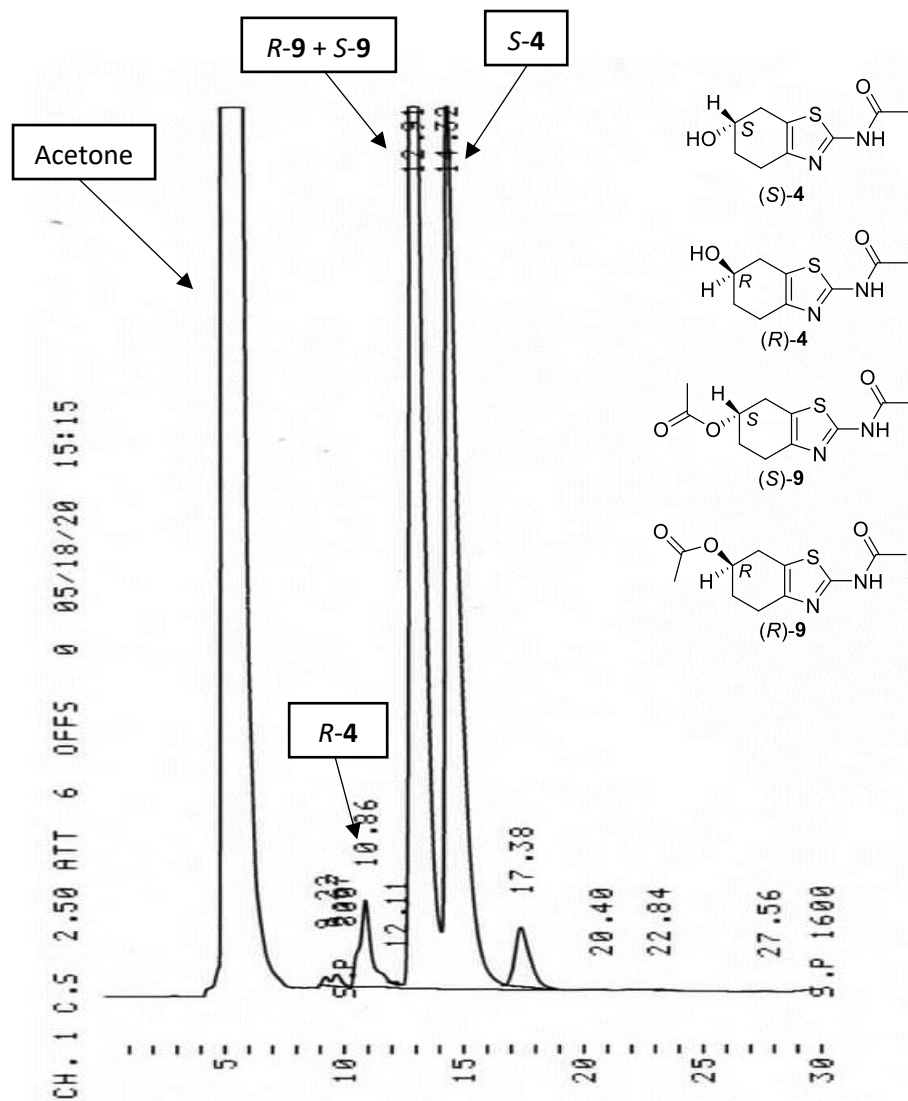


Figure S6. MS-MS of compound **9**



D-2500

05/18/20 15:15

METHOD:

TAG: 1 CH: 1

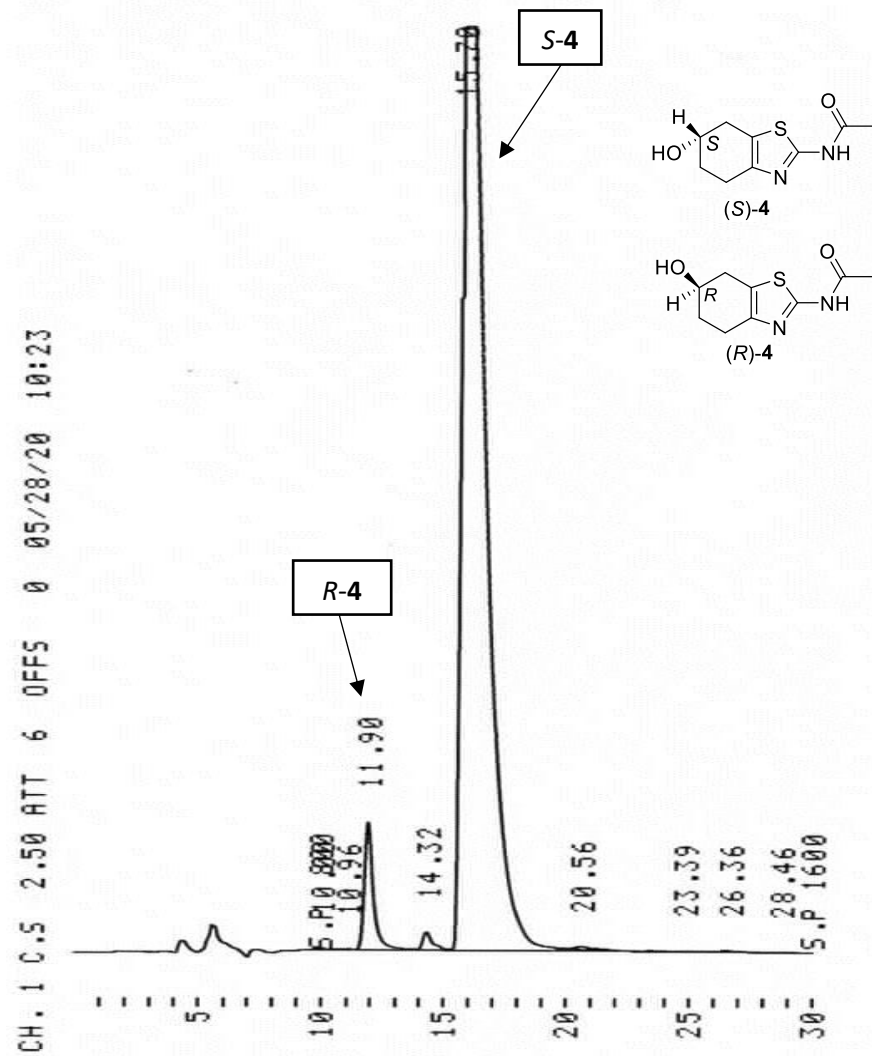
FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	9.22	8526	0.121	BU
2	9.67	18975	0.268	UB
3	10.86	231797	3.278	BU
4	12.11	1798	0.025	TBB
5	12.91	4002316	56.608	VU
6	14.32	2614438	36.978	VU
7	17.38	179840	2.544	TBB
8	20.40	4265	0.060	BB
9	22.84	5004	0.071	BB
10	27.56	3330	0.047	BB
TOTAL		7070289	100.000	

PEAK REJ : 0

RAW DATA STORAGE NO. 1

Figure S7. Lipase-catalyzed synthesis of enantioenriched (*S*)-*N*-(6-hydroxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide [(*S*)-4].
HPLC analysis of the crude reaction mixture



0-2500 05/28/20 10:23

METHOD: TAG: 6 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	10.00	3153	0.063	BU
2	10.96	4120	0.082	UU
3	11.90	234928	4.670	UU
4	14.32	35460	0.705	UU
5	15.70	4726830	93.965	UU
6	20.56	10358	0.206	TBB
7	23.39	5828	0.116	BU
8	26.36	6182	0.123	UB
9	28.46	3571	0.071	BB
TOTAL		5030430	100.000	

PEAK REJ : 0

RAW DATA STORAGE NO. 5

Figure S8. Lipase-catalyzed synthesis of enantioenriched (S)-N-(6-hydroxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide [(S)-4].
HPLC analysis of the purified (S)-4

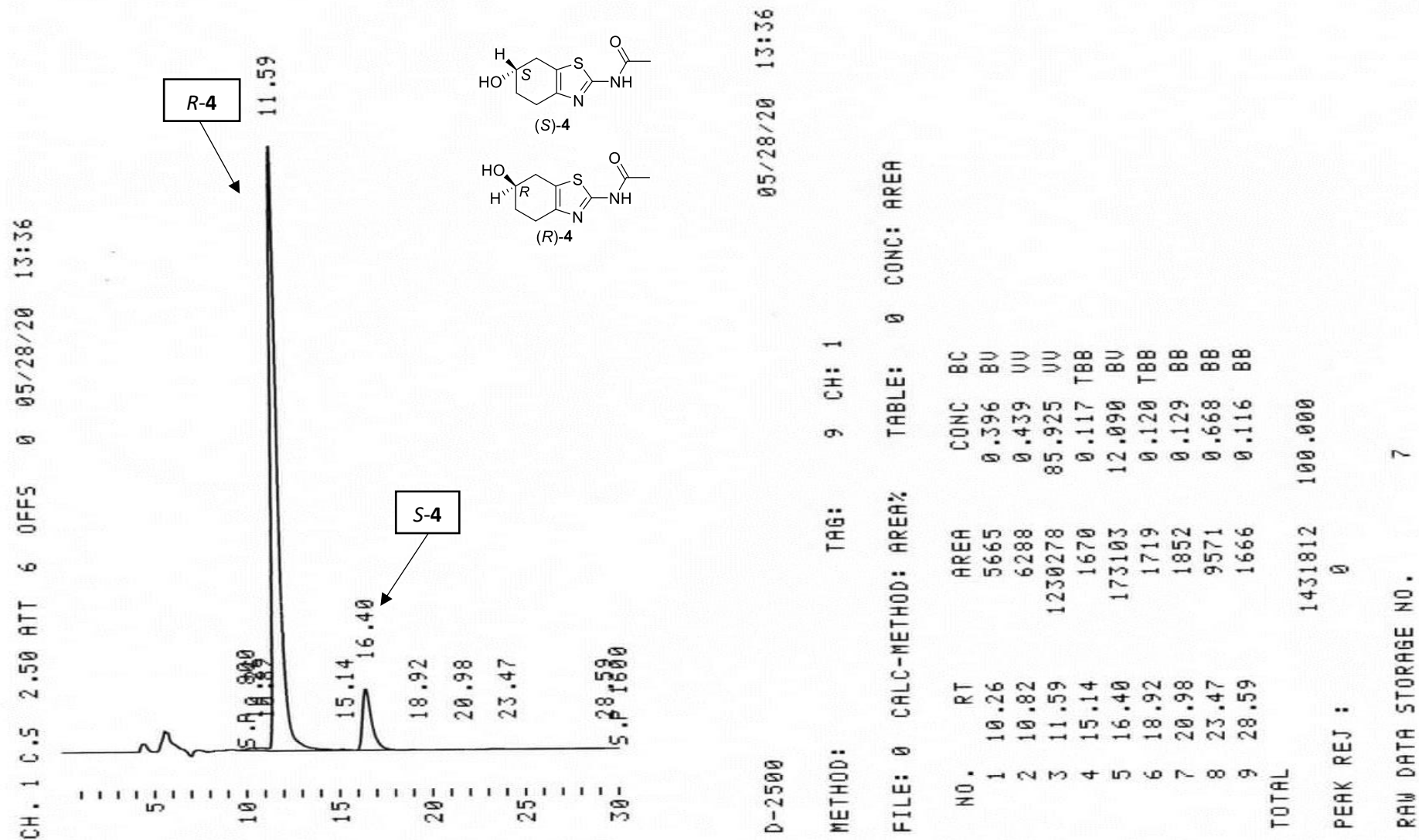


Figure 9. Lipase-catalyzed synthesis of enantioenriched (S)-N-(6-hydroxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide [(S)-4].
HPLC analysis of the purified and hydrolyzed (R)-9

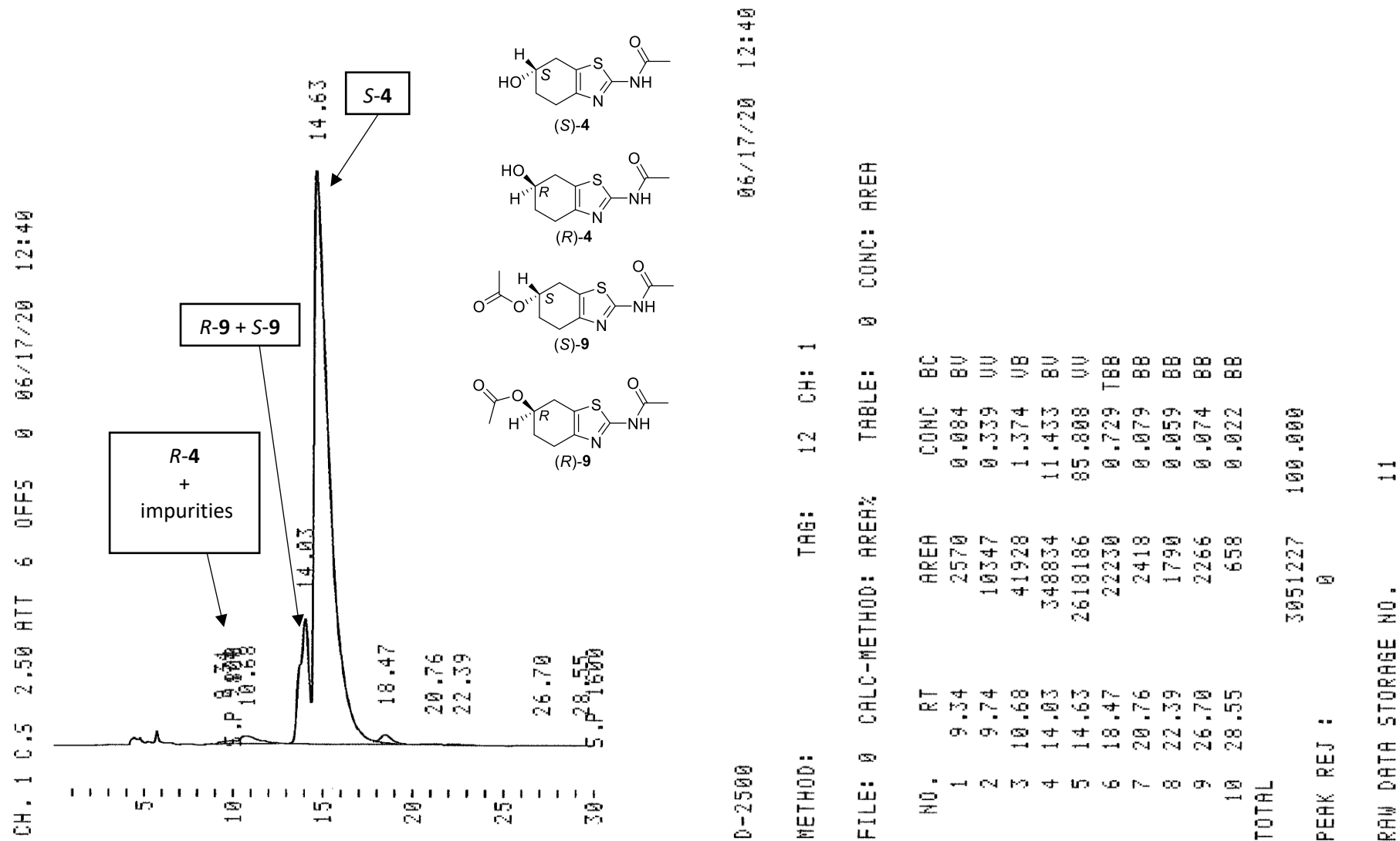


Figure S10. Lipase-catalyzed synthesis of enantiopure (S)-N-(6-hydroxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide [(S)-4].
HPLC analysis of the crude reaction mixture

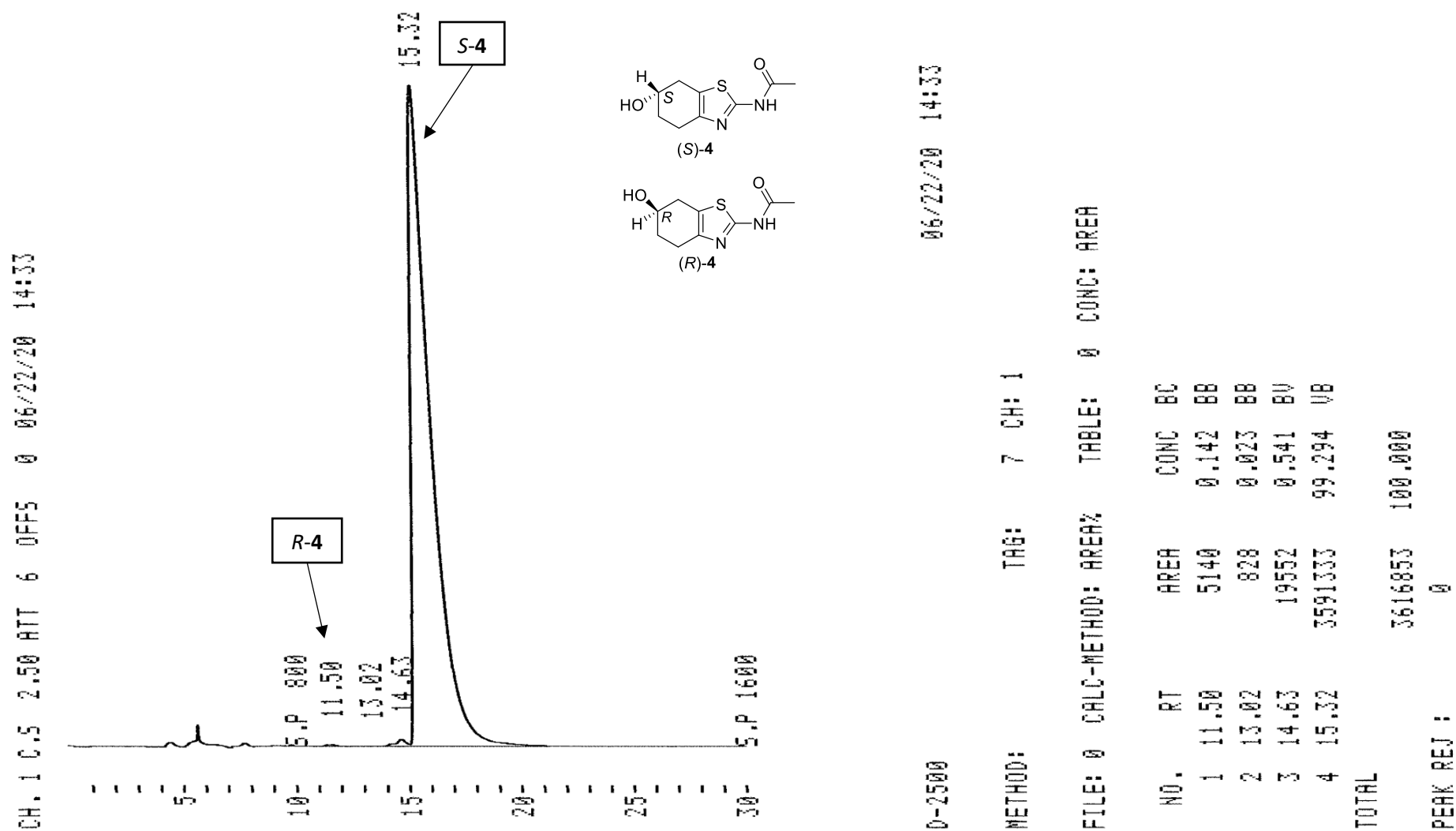


Figure S11. Lipase-catalyzed synthesis of enantiopure (S)-N-(6-hydroxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide [(S)-4].
HPLC analysis of the purified (S)-4

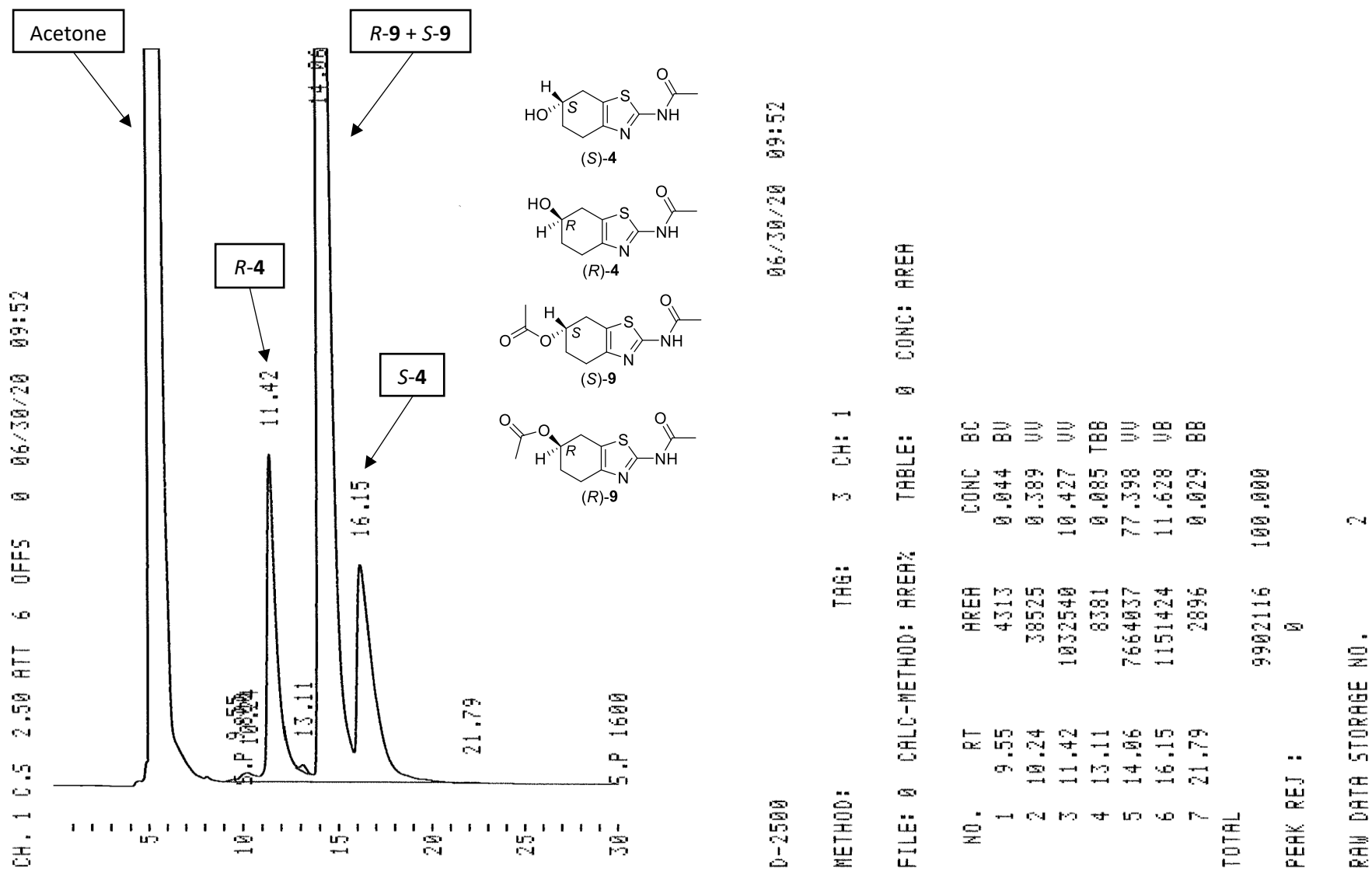


Figure S12. Lipase-catalyzed synthesis of enantiopure (*R*)-2-Acetamido-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl acetate [(*R*)-9].
HPLC analysis of the crude reaction mixture

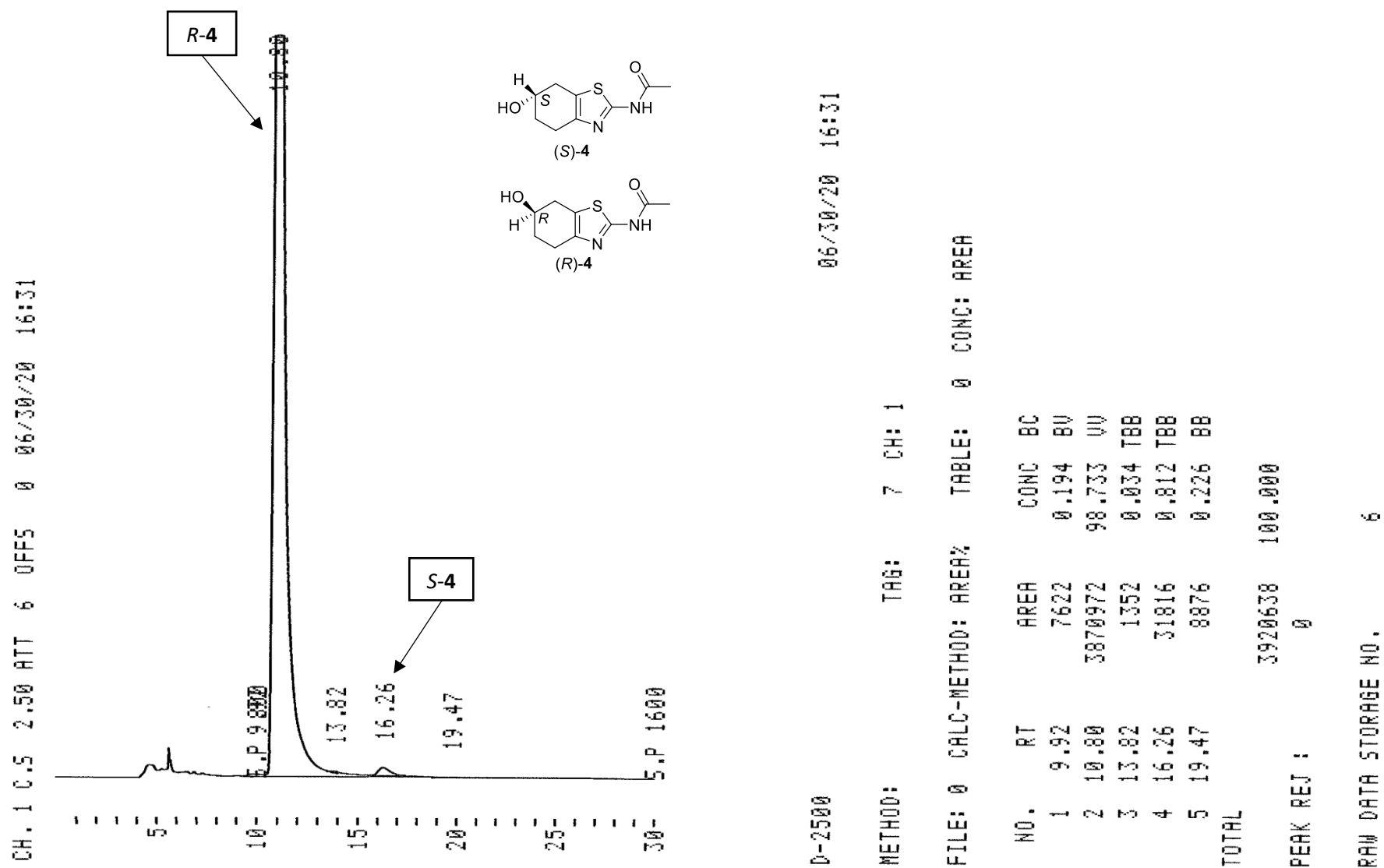


Figure S13. Lipase-catalyzed synthesis of enantiopure (R)-2-Acetamido-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl acetate [(R)-9].
HPLC analysis of the purified and hydrolyzed (R)-9